

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

EIGHTIETH MEETING
OF THE
CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

8:30 a.m.
Thursday, February 27, 1997

Jack Masur Auditorium
Building 10, Clinical Center
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland

APPEARANCES

COMMITTEE MEMBERS:

BARRY MASSIE, M.D., Chairman (present morning session)
Director, Coronary Care Unit
Department of Medicine
Veterans Administration Hospital
4150 Clement Street
San Francisco, California 94121

JOAN C. STANDAERT, Executive Secretary
Center for Drug Evaluation and Research
Food and Drug Administration
234 Summit Street, Room 117
Toledo, Ohio 43604

ROBERT CALIFF, M.D. (present afternoon session)
Professor of Medicine
Director, Duke Clinical Research Center
Duke University Medical Center
2024 West Main Street, Box 31123
Durham, North Carolina 27707

JOHN DiMARCO, M.D.
Professor of Medicine
Cardiovascular Division
University of Virginia Hospital, Box 158
Hospital Drive, 5th Floor
Private Clinic, Room 3608
Charlottesville, Virginia 22908

CINDY GRINES, M.D.
Director, Cardiac Catheterization
Division of Cardiovascular Disease
William Beaumont Hospital
3601 West Thirteenth Mile Road
Royal Oak, Michigan 48073-6769

MARVIN KONSTAM, M.D.
Professor of Medicine
New England Medical Center
750 Washington Street, Box 108
Boston, Massachusetts 02111

APPEARANCES

COMMITTEE MEMBERS: (Continued)

JoANN LINDENFELD, M.D. (present morning session)
Professor of Medicine
Division of Cardiology
University of Colorado Health Science Center
4200 East Ninth Avenue, B-130
Denver, Colorado 80262

LEMUEL MOYE, M.D., PH.D.
Associate Professor of Biometry
University of Texas Health Science Center
at Houston
Coordinating Center for Clinical Trials
1200 Herman Pressler Street, Suite 801
Houston, Texas 77030

CYNTHIA RAEHL, PHARM.D.
Consumer Representative
Chair, Pharmacy Department
School of Pharmacy
Texas Technical University
Health Science Center
1300 South Coulter Drive
Amarillo, Texas 79106-9711

DAN RODEN, M.D.C.M.
Vanderbilt University
Division of Clinical Pharmacology
532C Medical Research Building-1
23rd and Pierce Avenue
Nashville, Tennessee 37232-6602

UDHO THADANI, FRCP (present morning session)
Professor of Medicine
Division of Cardiology
Oklahoma University Health Sciences Center
920 S.L. Young Boulevard, 5-SP-300
Oklahoma City, Oklahoma 73104

MICHAEL WEBER, M.D.
Chairman, Department of Medicine

Brookville University Hospital Medical Center
1 Brookville Plaza
Brooklyn, New York 11212

APPEARANCES

COMMITTEE CONSULTANTS:

JEFFREY BORER, M.D.
ROBERT CODY, M.D. (present morning session)
RALPH D'AGOSTINO, PH.D.

FOOD AND DRUG ADMINISTRATION STAFF:

BOB FENICHEL, M.D.
RAYMOND LIPICKY, M.D.
NORMAN STOCKBRIDGE, M.D.
ROBERT TEMPLE, M.D.

MEDCO REPRESENTATIVES:

JAY COHN, M.D.
LLOYD FISHER, PH.D.
CESARE ORLANDI, M.D.
JOSEPH QUINN, M.S.P.H.

SMITHKLINE BEECHAM REPRESENTATIVES:

WILSON COLUCCI, M.D.
LLOYD FISHER, PH.D.
MILTON PACKER, M.D.
ROBERT L. POWELL, PH.D.
NEIL SHUSTERMAN, M.D.
JIM TIEDE, PH.D.

C O N T E N T S
MORNING SESSION

NDA 20-727, BIDIL
(hydralazine HCl and isosorbide dinitrate)
to be indicated for congestive heart failure

AGENDA ITEM	PAGE
OPEN PUBLIC HEARING	7
MEDCO RESEARCH, INC. PRESENTATION:	
Introduction by Dr. Cesare Orlandi	11
Historical Overview, Clinical Efficacy by Dr. Jay Cohn	12
Statistical Overview by Dr. Joseph Quinn	32
Summary/Conclusions by Dr. Jay Cohn	44
COMMITTEE REVIEW AND DISCUSSION	114

C O N T E N T S
AFTERNOON SESSION

NDA 20-297 s-001, COREG (carvedilol)
to be indicated for congestive heart failure

AGENDA ITEM	PAGE
SMITHKLINE BEECHAM PRESENTATION	
Introduction - by Dr. Robert Powell	205
Clinical Program - by Dr. Neil Shusterman	213
COMMITTEE REVIEW AND DISCUSSION	303

P R O C E E D I N G S

(8:30 a.m.)

DR. MASSIE: I want to welcome everybody to the 80th meeting of the Cardio-Renal Advisory Panel which we're going to have today.

Before getting started, let me briefly just introduce the members of the committee who are sitting from my left to my right: Dr. Dan Roden, Dr. Marvin Konstam, Dr. Cynthia Raehl, Dr. Michael Weber, Dr. Lemuel Moye, Dr. JoAnn Lindenfeld, our Secretary, Joan Standaert, Dr. DiMarco, Dr. Rob Califf, Dr. Udho Thadani, and not yet but to come later, Dr. Cynthia Grines. Dr. Lipicky representing the Division of Cardio-Renal Drugs is on the far left, and I guess Dr. Temple will be joining us.

In addition, we have several outside consultants for today's meeting. Dr. Ralph D'Agostino, who will be a voting member as a special government employee, as will Dr. Jeffrey Borer, and Dr. Robert Cody is our special consultant, but unfortunately not able to vote.

The first order of business is that we are open for public comment. If anybody has any comments, we'd be happy to entertain them at this time.

In the absence of public comment, we can proceed with our business. Joan Standaert is going to

1 discuss the waivers and potential conflicts of interest of
2 the committee members.

3 MS. STANDAERT: The following announcement
4 addresses the issue of conflict of interest with regard to
5 this meeting and is made a part of the record to preclude
6 even the appearance of such at this meeting.

7 Based on the submitted agenda for the meeting
8 and all financial interests reported by the committee
9 participants, it has been determined that all interests in
10 firms regulated by the Center for Drug Evaluation and
11 Research present no potential for an appearance of a
12 conflict of interest at this meeting, with the following
13 exceptions.

14 In accordance with 18 U.S.C. 208(b), full
15 waivers have been granted to Drs. Barry Massie, Lemuel
16 Moye, and Dr. Robert Califf, which permit them to
17 participate in all official matters concerning Posicor. In
18 addition, Dr. Dan Roden and Dr. Udho Thadani are excluded
19 from participating in all official matters concerning
20 Posicor.

21 Further, in accordance with 18 U.S.C.
22 208(b)(3), a limited waiver has been granted to Dr. Udho
23 Thadani.

24 I'm sorry. I'm reading the wrong announcement.

1 Well, I'll start over again. Sorry, excuse me. We'll do
2 that again tomorrow.

3 This is the announcement for February 27th,
4 1997. The following announcement addresses the issue of
5 conflict of interest with regard to this meeting and is
6 made a part of the record to preclude even the appearance
7 of such at this meeting.

8 Based on the submitted agenda for the meeting
9 and all financial interests reported by the committee
10 participants, it has been determined that all interests in
11 firms regulated by the Center for Drug Evaluation and
12 Research present no potential for an appearance of a
13 conflict of interest at this meeting, with the following
14 exceptions.

15 In accordance with 18 U.S.C. 208(b)(3) full
16 waivers have been granted to Drs. JoAnn Lindenfeld, Lemuel
17 Moye, Marvin Konstam, and Dr. Dan Roden, which permit them
18 to participate in all official matters concerning BiDil.
19 In addition, Dr. Robert Califf is excluded from
20 participating in all official matters concerning BiDil.
21 Further, in accordance with 18 U.S.C. 208(b)(3), a waiver
22 has been granted to Dr. Marvin Konstam, which permits him
23 to participate in all official matters concerning Coreg.

24 However, Drs. Barry Massie, JoAnn Lindenfeld,

1 and Dr. Udho Thadani are excluded from participating in all
2 official matters regarding Coreg.

3 Copies of the waiver statements may be obtained
4 by submitting a written request to the agency's Freedom of
5 Information Office, Room 12A-30 of the Parklawn Building.

6 We would also like to disclose for the record
7 that Dr. Robert Califf and his employer, the Duke
8 University Medical Center, have interests which do not
9 constitute a financial interest within the meaning of 18
10 U.S.C. 208(a), but which could create the appearance of a
11 conflict.

12 The agency has determined that notwithstanding
13 these involvements, that the interest of the government in
14 Dr. Califf's participation outweighs the concern that the
15 integrity of the agency's programs and operations may be
16 questioned. Therefore, Dr. Califf may participate in all
17 official matters concerning Coreg.

18 With respect to FDA's invited guest expert, Dr.
19 Robert J. Cody has reported interests which we believe
20 should be made public to allow the participants to
21 objectively evaluate his comments. Dr. Cody would like to
22 disclose that he has conducted clinical trials and
23 consulted for SmithKline Beecham, Merck, and Zeneca. He
24 has also given presentations which were sponsored by

1 SmithKline Beecham, and Merck.

2 In the event that the discussions involve any
3 other products or firms not already on the agenda for which
4 an FDA participant has a financial interest, the
5 participants are aware of the need to exclude themselves
6 from such involvement and their exclusion will be noted for
7 the record.

8 With respect to all other participants, we ask
9 in the interest of fairness that they address any current
10 or previous financial involvement with any firm whose
11 products they may wish to comment upon.

12 That concludes the statement for February 27th,
13 1997.

14 DR. MASSIE: Thank you very much, Joan.

15 Well, as is probably apparent to all the
16 members of this audience, as well as all the committee
17 members, we have a very full agenda today and I'm going to
18 do my best to keep the first half on time. In the interest
19 of trying to proceed smoothly, I'm going to ask the
20 committee members to try not to interrupt the sponsor's
21 presentation midstream because we will allow a block of
22 time for questions thereafter and I think that will allow
23 the information to flow more smoothly.

24 So, I guess we are ready for the presentation

1 for BiDil, NDA 20-727.

2 DR. ORLANDI: Dr. Massie, members of the
3 committee, Dr. Lipicky, ladies and gentlemen, good morning.

4 We are here today to present you BiDil for the
5 treatment of congestive heart failure. BiDil is a
6 formulation of two drugs you are very familiar with,
7 hydralazine and isosorbide dinitrate.

8 Our application is based on two landmark
9 clinical trials conducted in the 80s by the Veterans
10 Administration, the V-HeFT I and V-HeFT II studies. Based
11 on the results of these studies, we propose that BiDil is
12 useful in the treatment of congestive heart failure as an
13 adjunct to digitalis and diuretics. It is our opinion also
14 that it's most appropriate the use of this formulation in
15 patients that are not taking ACE inhibitors, which have
16 become also part of standard therapy.

17 Dr. Jay Cohn, who led the V-HeFT trials effort,
18 will provide a historical overview of the trials. Mr. Joe
19 Quinn will then address specific statistical issues that
20 have been raised by the agency. And Dr. Cohn will also
21 conclude our presentation with a brief summary of the
22 findings.

23 I just wanted to mention briefly that we have a
24 number of consultants in the audience to address any

1 specific question that the committee may have. This list
2 includes Dr. Lloyd Fisher, who conducted a re-analysis of
3 the V-HeFT trials, Dr. Uri Elkayam, Dr. Krik Adams, Dr. Ho-
4 Leung Fung, and Dr. Alan Forrest.

5 Dr. Cohn?

6 DR. COHN: Thank you very much, Cesare, and I'd
7 like to express my appreciation to the FDA and to the
8 committee for giving me the opportunity to review with you
9 the trials that we initiated really almost 20 years ago
10 with the planning of the first V-HeFT trial, the
11 vasodilator heart failure trials, which have continued to
12 date, and the results of these first two trials will be the
13 basis for our discussion this morning.

14 What we would like to propose to you at the end
15 of this presentation is that there is a strong basis for
16 approval of BiDil for heart failure and we would propose
17 that this be based on a survival benefit for BiDil as
18 compared to placebo, on the basis of a strong trend from
19 proved exercise tolerance versus both placebo and versus
20 Enalapril in these two trials, on the basis of a sustained
21 increase in ejection fraction that we believe not only
22 confirms the mechanism of action of this drug combination
23 but also confirms that there is a long-term effect of this
24 drug combination.

1 This combination of therapy has a well
2 established rationale and an even better rationale today
3 than at the time these studies were initiated, and we'll go
4 into that in the course of this presentation.

5 The safety of this drug combination of these
6 two long-used agents is well established.

7 This combination is already widely recommended
8 as a treatment option in essentially all of the treatment
9 guidelines that have been published in the last few years.

10 And the approval of this combination is
11 required to provide prescribing information to physicians
12 who have been told to use this drug combination.

13 Now then, hydralazine and isosorbide dinitrate
14 were first used in combination. We did this, and Joe
15 Franciosa, who worked with me at that time, is in the
16 audience here today. We did this on the basis of the
17 potency of this combination as a vasodilator, and the
18 dramatic acute hemodynamic effect that this drug
19 combination produced.

20 At that time we predicted that this favorable
21 hemodynamic effect might be translated into a long-term
22 benefit but there were no long-term data available in order
23 to determine that. V-HeFT, then, was organized as a
24 landmark heart failure study, the first mortality trial

1 undertaken in heart failure, with a goal to assess long-
2 term efficacy of this vasodilator therapy added to
3 conventional therapy, which at that time was digitalis and
4 diuretics. ACE inhibitors had not been developed at that
5 time.

6 And it was possible, of course, at that time to
7 include a placebo group because there was no other
8 effective therapy, and this provided the first and, I must
9 say, the only data that will exist either now or in the
10 future of digitalis-diuretic therapy with placebo added in
11 long-term therapy of heart failure.

12 We would suggest that the impact of the
13 findings of V-HeFT are that there is now demonstrated
14 efficacy of chronic therapy, and this was indeed the first
15 therapy which was demonstrated to be effective, and it has
16 provided a new treatment option for the management of the
17 patient with heart failure, which has already been accepted
18 by most guideline committees.

19 Well, V-HeFT I was a trial assessing
20 vasodilator therapy in long-term therapy compared to
21 placebo, added to, as I pointed out, digoxin and diuretic
22 therapy for patients with heart failure. The two
23 vasodilator regimens that were employed in this study were
24 the hydralazine isosorbide dinitrate combination, and an

1 alternate vasodilator, Prazosin, which had a rather similar
2 hemodynamic effect in this patient population when given
3 acutely.

4 The comparison of the survival times between
5 the placebo arm and the vasodilator arms was proposed to
6 use a one-sided hypothesis because there was no reason at
7 that point to consider any adverse effect of this therapy.
8 The question was, is the therapy effective. So, it was a
9 one-sided hypothesis, and therefore one-sided tests were
10 proposed.

11 V-HeFT II was initiated after the completion of
12 V-HeFT I, and it was undertaken to determine whether the
13 effective arm in V-HeFT I, that is the hydralazine-
14 isosorbide dinitrate arm, had an effect comparable or
15 different from that of Enalapril, which at that point in
16 time had already been evaluated for short-term therapy of
17 heart failure and it appeared to be effective. These drugs
18 then were added to pre-existing conventional therapy of
19 digoxin and diuretic.

20 No placebo arm was included in V-HeFT II
21 because it was felt by the planning committee that it was
22 unethical after the results of V-HeFT I to have a placebo-
23 treated group for long-term therapy. And since it was not
24 known which of the two treatment arms would be more

1 beneficial, it was a two-sided hypothesis and two-sided
2 tests that were employed.

3 Now, these trials that I'm going to tell you
4 about were both randomized, double-blinded. One was
5 placebo-controlled, the other had a positive control. All
6 patients were followed for at least 6 months after
7 randomization into the trial, and the survival status was
8 confirmed in all patients at the planned date of completion
9 of the trial. Both of these trials were planned to be
10 completed at a specific date, and that date was indeed
11 utilized in termination of the trial.

12 The inclusion criteria were all males. The
13 studies were all performed in Veterans Affairs hospitals.
14 They were males between the ages of 18 and 75. They had a
15 history of heart failure, with limitation of exercise
16 tolerance for at least 3 months prior to screening. They
17 all remained symptomatic, despite the use of digoxin and
18 diuretics, and they had objective measurements that made
19 them eligible. That is, there was cardiac dysfunction, as
20 defined by either an enlarged heart on chest x-ray, greater
21 than .55 cardiothoracic ratio, or a radionuclide ejection
22 fraction of less than 45 percent, or a dilated left
23 ventricle on echocardiography with a left ventricular
24 internal dimension and diastole of greater than 2.7

1 centimeters per meter squared. These criteria were used in
2 both trials.

3 In addition, the patients were all subjected to
4 a bicycle ergometer exercise test with measurement of gas
5 exchange. And they had to have a reduced peak oxygen
6 consumption less than 25 ml per kilogram per minute to be
7 eligible for the trial.

8 The major endpoint in both trials was survival
9 time, and two related endpoints were utilized. That is,
10 the overall survival, and of course the 2-year survival.
11 Of course, the reason for doing that is that if one follows
12 patients long enough, everyone will die and it was thought
13 that perhaps a 2-year endpoint might be a more sensitive
14 marker for a favorable effect of the therapy. So, these
15 were both proposed as analytical endpoints.

16 Now, the survival time was proposed to be
17 carried out by the log-rank test, with the addition of a
18 Cox proportional hazards model, using baseline patient
19 characteristics as modifiers for the Cox model.

20 I will, in addition, talk to you about two major
21 endpoints of the trial, secondary endpoints, at least.
22 That is, changes in left ventricular ejection fraction and
23 changes in peak oxygen consumption, both of which are the
24 major determinants of survival in this population. These

1 two endpoints were selected by the FDA with its consultant
2 Milton Packer, and Milton is in the audience if there are
3 any questions about his selection of these two as two of
4 the criteria on which to adjust the mortality with the Cox
5 analysis.

6 These, we all agree, are major endpoints in the
7 management of heart failure, so that these two I will talk
8 to you about in some detail. These were assessed by
9 repeated measures analysis, and the t-test of change from
10 baseline by individual visits was utilized for statistical
11 analysis.

12 Well, these are the patient characteristics in
13 the two trials. I think you can see that the
14 characteristics in the two patient populations are quite
15 similar. That is, the patients were somewhere between 58
16 and 60 years old, a little older in V-HeFT II. The study
17 was obviously performed later. The ejection fraction
18 ranged around 28 to 29 or 30 percent in both trials. The
19 cardiothoracic ratio exhibited an enlarged heart in both
20 studies. The peak oxygen consumption averaged around 15 or
21 14 ml per kilogram per minute, and patients all had heart
22 failure for at least 2 or 3 years.

23 The majority of the patients were Caucasian.
24 That is, about 70 percent of them in both trials, but there

1 was a fairly sizeable number of African-Americans in the
2 trial. We won't go into that, but we have much data
3 comparing the Caucasian and African-American responses.

4 This is the duration of heart failure, which
5 predominantly was between 6 and 48 months. About 55
6 percent of the patients had coronary disease as the
7 etiology of their heart failure, and about 45 percent had
8 what was thought to be non-ischemic cardiomyopathy.

9 Now, this was the major endpoint of the trial,
10 which was to monitor mortality, and I plot here the
11 differences between the placebo and the hydralazine-
12 isosorbide dinitrate groups during the 4-plus years in
13 which the patients were followed. You can see that at the
14 initiation there were 273 placebo patients and 186
15 hydralazine-isosorbide dinitrate patients. That was a
16 planned preference for placebo entrance because we had a
17 third treatment arm, which was Prazosin, which I don't have
18 plotted here. I'll show you the survival curves, including
19 Prazosin, in a moment. But this was an attempt to have a
20 larger placebo group so that we could have more confidence
21 in the placebo arm.

22 You can see at the end of 1 year, there had
23 been a 19.5 percent mortality in the placebo arm, and a
24 12.1 percent mortality with H/ISDN, and that was a 38

1 percent mortality reduction.

2 At the end of 2 years, the differences were 34
3 and 25.6 percent, or a 25 percent reduction. At 3 years
4 the reduction was at 23 percent, and by 4 years it was a
5 little under 10 percent. By 5 years, of course, the
6 numbers became very small. So, after 3 years we really
7 have very little power and obviously an instability of the
8 survival curves at that point in time.

9 This indeed is a plot of the three survival
10 curves in V-HeFT I. H/ISDN in yellow at the top showing
11 that there is a clear reduced mortality or improved
12 survival in this treatment compared to the placebo group in
13 blue. The Prazosin group in red, superimposes on the
14 placebo group until this very terminal end, where there's
15 great instability in the numbers.

16 I think this was the first evidence that a
17 potent vasodilator, which Prazosin is, is not necessarily
18 effective in heart failure, so the original concept that
19 the two vasodilator arms would behave similarly was
20 contradicted by this study. We now know that the efficacy
21 of the vasodilator chronically is not necessarily related
22 to its hemodynamic effect.

23 This is just a brief summary of the statistical
24 analysis of this trial. You'll hear a good deal more about

1 this later from Joe Quinn, but just to briefly tell you
2 what the statistics were. Using the log-rank test, the 2-
3 year mortality reduction from hydralazine and nitrate
4 compared to placebo was .0279, and the risk ratio .7. And
5 as you can see, the 95 percent confidence intervals did not
6 overlap 1.

7 When the Cox model was employed, using the
8 three variables that were chosen by the FDA and its
9 independent consultant to be employed to adjust the log-
10 rank test, the p value fell to .0168 and again, the
11 confidence interval did not overlap 1.

12 Overall mortality by the log-rank test was a p
13 value of .046, and the confidence interval did include 1.
14 When the Cox model was employed, that fell to .0177 and the
15 confidence interval did not overlap 1.

16 DR. MOYE: One question to clarify. Can you go
17 back to the previous slide, please?

18 DR. COHN: Yes, sure, Lem.

19 DR. MOYE: When you show the log-rank p value
20 of .046, now say again what the threshold was that the
21 investigators determined prospectively for stat
22 significance here.

23 DR. COHN: Oh, we'll get into that a good deal
24 later. I'm just showing you the raw p values with no

1 intent to suggest that this has met any criteria that was
2 established. So, we'll get into that in more detail later
3 on. These are the raw numbers.

4 Now, the other major endpoints that I wanted to
5 bring to your attention were the peak oxygen consumption
6 and the ejection fraction. This is the intent-to-treat
7 analysis of changes in peak oxygen consumption over time in
8 the two treatment arms of interest. There was clearly a
9 trend, but no statistical difference between the two. A
10 trend for the H/ISDN group to exhibit sustained improvement
11 in peak oxygen consumption, which did not occur in the
12 placebo arm, but none of these differences were
13 statistically significant.

14 Now, V-HeFT I gas exchange was done by a
15 primitive methodology that we developed ourselves and we
16 put some instruments together. There was no commercial
17 instrument at that point available for use. It was a
18 mixing chamber. It was a pretty crude way to measure peak
19 oxygen consumption.

20 V-HeFT II, that I'll show you in a moment, was
21 carried out with modern technology with breath-by-breath
22 gas exchange data, so that I have more confidence in the
23 V-HeFT II gas exchange data.

24 However, the protocol said that exercise tests

1 would only be included for analysis if they were terminated
2 by dyspnea or fatigue. And therefore, in the protocol
3 analysis, there were fewer patients included because those
4 who had orthopedic reasons, et cetera, for not finishing an
5 exercise test were excluded.

6 When we did that, the data looked pretty
7 similar. That is, the green line, which is H/ISDN,
8 exhibited some improvement, which seemed to be at least
9 unchanged or improved over time. The placebo group in blue
10 exhibited what was a trend toward a decline. And one time
11 point, at 1 year, exhibited a significant p value of less
12 than .05 for the improvement of exercise performance in the
13 H/ISDN group compared to the placebo group.

14 That might be shown even a little more clearly
15 on this next slide, in which we have done an analysis
16 looking at the changes in exercise performance by groups.
17 So, this represents in the placebo group on the left and
18 the H/ISDN group on the right all patients who reached 1
19 year after randomization and what their exercise tests
20 showed.

21 First of all, there were more people who died
22 in the placebo group. This has already been pointed out.
23 So, this excluded them from a repeat exercise test, and
24 more were excluded in the placebo arm.

1 Then we've looked at three different levels of
2 peak oxygen consumption, using .07 ml per kilogram per
3 minute as the dividing point because the mean increase in
4 the H/ISDN group was 0.7 at 1 year.

5 You can see that in purple are those whose
6 exercise performance worsened over that 1-year period of
7 time, and there were fewer here than here.

8 In yellow are those whose exercise performance
9 stayed the same between the two, and there were more people
10 in this group than in this group.

11 In this top bar are those whose exercise
12 performance improved over that period of time, and there
13 were more here than there were in the placebo group. And
14 these are the ones who, for administrative reasons, had
15 missing data and they were equal in the two treatment arms.

16 By a chi-square analysis of these two
17 distributions it's significant at the p .024 level.

18 Now, the ejection fraction changes were very
19 dramatic and consistent. That is, H/ISDN produced a
20 significant and sustained improvement in ejection fraction.
21 These are all measured by radionuclide techniques
22 sequentially. In contrast, the placebo group exhibited no
23 improvement and a progressive decline over time, which did
24 not occur in this group.

1 I personally view the sustained improvement of
2 ejection fraction as a structural alteration in the left
3 ventricle with reduction of the remodeling process, which
4 appears to progress in the placebo group.

5 Now, this slide adds the Prazosin group to this
6 analysis. The Prazosin group now is in blue and the
7 placebo group in yellow. You can see that these two track
8 together, and there was a progressive decline of ejection
9 fraction in both groups, indicating that this vasodilator,
10 Prazosin, did not favorably affect the structure remodeling
11 process in the left ventricle, whereas this vasodilator,
12 H/ISDN, did.

13 This indeed tracks directly with the mortality
14 results that I've shown you before, and we have data that I
15 won't have time to go into to suggest to you that the
16 changes in ejection fraction are indeed very powerful
17 predictors of the change in mortality in the individual
18 patient groups.

19 Well, when we completed V-HeFT I, there had
20 been also the publication of data from the CONSENSUS study
21 done in northern Scandinavia, in class 4 heart failure,
22 using Enalapril as the treatment option. That study
23 eventually led to the approval of Enalapril for mortality
24 reduction in heart failure. And that was a 1-year trial,

1 so that at the end of 1 year, in CONSENSUS, this was the
2 mortality in the placebo group, very high because these
3 were class 4 heart failure patients, and this was the
4 mortality in the Enalapril group at 1 year, and that
5 represented a 31 percent reduction.

6 When we looked at the V-HeFT data in terms of
7 1-year data, this was the reduction from 20 percent to 13
8 percent which represented a 38 percent reduction in
9 mortality. We thought that these two reductions were quite
10 comparable, but this was indeed a very different patient
11 population than V-HeFT and we therefore asked the question,
12 would Enalapril have the same beneficial effect, or greater
13 beneficial effect in mild to moderate heart failure as did
14 hydralazine and isosorbide dinitrate in V-HeFT I, and that
15 was the basis for the design of V-HeFT II.

16 These were the survival curves from V-HeFT II,
17 Enalapril in green, H/ISDN in yellow, and you can see that
18 there was a clear trend for improved survival with
19 Enalapril, compared to hydralazine and isosorbide
20 dinitrate.

21 This is the statistical analysis in brief of
22 that difference by log-rank test, and a two-sided p value
23 here. The p was .017 for the 2-year mortality difference
24 between the two, favoring Enalapril, with a risk ratio of

1 1.46.

2 The overall mortality difference did not
3 achieve statistical significance, .0828, but a clear trend
4 for a favorable effect of Enalapril compared to H/ISDN.
5 But here the confidence intervals overlap 1.0.

6 The other endpoints, again, in V-HeFT II are
7 striking. This was the intent-to-treat changes in oxygen
8 consumption during exercise, and once again, H/ISDN
9 exhibited a modest but sustained improvement in peak oxygen
10 consumption, certainly for the first two years, and at
11 least three time points these increases, when compared to
12 the changes with placebo, were statistically significant --
13 not placebo -- Enalapril, I'm sorry, were statistically
14 significant. At no time point during follow-up did
15 Enalapril produce an improvement in peak oxygen
16 consumption. In fact, oxygen consumption tended to decline
17 over time.

18 Now, this was the intent-to-treat analysis, but
19 the protocol analysis, again, defined the changes to be
20 identified only in patients who stopped exercising for
21 dyspnea or fatigue, and this is the protocol analysis,
22 showing pretty much the same thing, that there was a strong
23 trend for an improvement with H/ISDN and not with
24 Enalapril. These were the statistically significant

1 points.

2 I must emphasize to you that at 3 months and at
3 6 months, which represents the time frame for which the FDA
4 has all existing data on changes in exercise and heart
5 failure therapy, H/ISDN exhibited significant improvement
6 in peak exercise capacity compared to Enalapril. I think
7 that if the study therefore had been terminated at 6
8 months, as have most other exercise studies, there would
9 have been no question that this therapy was more effective
10 than the ACE inhibitor in symptom relief or exercise
11 performance in heart failure.

12 Now, once again, the ejection fraction changes
13 were very striking with both therapies. That is, both
14 Enalapril in green and H/ISDN in yellow produced a sizeable
15 and sustained improvement in ejection fraction. In fact,
16 at 3 months the increase in the H/ISDN group was greater
17 than the increase in the Enalapril group. Thereafter the
18 two were similar, suggesting that both interventions
19 favorably affect the remodeling process in the left
20 ventricle.

21 Now, we were struck when we completed V-HeFT
22 II, and we had the same treatment arm in both trials --
23 that is the H/ISDN arm was exactly identical and the
24 therapy was identical in the two trials. The survival

1 curves for these two treatment arms were superimposable.
2 That implied to us that there must have been some stability
3 in this response since it was so reproducible.

4 Now, this of course then comes to the placebo
5 arms because we did not repeat a placebo in V-HeFT II and
6 therefore, we are dependent on the placebo group in V-HeFT
7 I. I have given you a list here of the so-called placebo
8 groups in more recent heart failure trials. I have given
9 you data on the number of deaths in these trials, in the
10 placebo arms, the duration of follow-up, and the use of
11 what may be critical co-therapy. That is, the use of
12 nitrates and the use of ACE inhibitors.

13 In V-HeFT I there were 120 deaths, so this is a
14 rather robust sample. The follow-up was 2.3 years. None
15 of the patients in the placebo arm received nitrates, and
16 none of them received ACE inhibitors. This is a true
17 placebo group, added to digoxin and diuretic therapy.

18 CONSENSUS, that I have already alluded to, had
19 only 55 deaths in the placebo arm. The follow-up averaged
20 only 0.5 years. 45 percent of those patients were treated
21 with a nitrate, which obviously potentially contaminates
22 the placebo group.

23 In the SOLVD trial, which is the largest
24 clinical experience in heart failure trials, there were 510

1 deaths in the placebo arm, and a follow-up of 3.4 years,
2 which makes this a very robust placebo group. But it isn't
3 a placebo group because 45 percent of these patients were
4 treated with nitrates chronically, and 23 percent in the
5 placebo group were given ACE inhibitors as drop-in therapy.
6 So, this is certainly not a placebo group.

7 Now, the more recent trials, PROMISE, which
8 exhibited an adverse effect of milrinone in heart failure,
9 had 127 deaths in the placebo group, an average follow-up
10 of only 0.5 years. But 59 percent of that placebo group
11 was treated with nitrates, and essentially all of them at
12 least were by protocol on ACE inhibitor. We don't have the
13 actual data in the paper.

14 The Vesnarinone trial, which was not replicated
15 by the more recent VEST study, have only 33 deaths in the
16 initial Vesnarinone mortality trial in the placebo arm.
17 The follow-up was only 0.5 years. We don't know about
18 nitrates, but 90 percent of the placebo group were on ACE
19 inhibitors.

20 The more recent Carvedilol American data that
21 you'll be reviewing later this morning, in the placebo
22 group there were 31 deaths. As you know, the follow-up was
23 only 0.5 years, but once again, 32 percent of them were
24 receiving nitrates and essentially all of them were

1 receiving an ACE inhibitor.

2 So, this is to point out to you that we will
3 never again have a placebo arm comparable to V-HeFT I
4 because it is ethically indefensible to any longer treat
5 patients without an ACE inhibitor, and we would like to
6 suggest that after today's meeting it would be equally
7 indefensible to treat them without a nitrate along with
8 hydralazine.

9 Well, if we can use that placebo arm, then, as
10 a comparator, we can put a plot of the five treatment arms
11 from V-HeFT, and in fact this analysis was recommended by
12 the FDA for us to do. So, this is in response to their
13 raising the issue about comparing the V-HeFT I placebo
14 group here in red with Enalapril in blue and with the two
15 hydralazine-isosorbide dinitrate curves in yellow.

16 Now, a 2-year endpoint was indeed a pre-study
17 endpoint, so we have dropped a vertical at 2 years in the
18 placebo arm, and discovered this is the mortality at 2
19 years and we put a horizontal line over to this mortality,
20 which is about 65 percent.

21 Then we determined at what time point would you
22 reach that same mortality if you had instead been treated
23 with hydralazine and isosorbide dinitrate, and these two
24 curves, which were just superimposed, show you that there

1 is a prolongation of life by an average of about 10 months.

2 If instead we had used Enalapril, the
3 prolongation of life would have been longer, at maximum
4 probably another 8 months. Obviously the effect is more
5 than 50 percent of this effect, and this effect is enhanced
6 by the fact that there was a little blip on that Enalapril
7 curve there, but be that as it may, it's clear that
8 Enalapril had a more favorable effect than did hydralazine
9 and isosorbide dinitrate. But both are very importantly
10 better than the placebo or Prazosin arms shown here.

11 Well, in summary, then, I've told you that
12 mortality is reduced by H/ISDN, that there is a strong
13 trend for improved exercise tolerance by H/ISDN, and that
14 there is sustained improvement in ejection fraction with
15 H/ISDN.

16 Now, a number of statistical issues have been
17 raised by the FDA, and I'll now turn the podium over to Joe
18 Quinn, who will address some of these issues. Joe?

19

20 DR. QUINN: Thank you, Dr. Cohn, and good
21 morning to everyone.

22 I would like to discuss several important
23 statistical issues that have been raised by the agency that
24 potentially impact the interpretation of the nominal p

1 values in the application.

2 The first issue is the impact of the interim
3 analysis. This slide summarizes the interim results of the
4 overall survival time that were provided to the V-HeFT I
5 Operations Committee.

6 Note that even though the protocol specified --
7 sorry. This slide summarizes the interim results of the
8 overall survival time that were provided to the V-HeFT I
9 Operations Committee. Note that even though the protocol
10 specified a one-sided test hypothesis, the p values shown
11 are two-sided p values, as the committee wanted to be
12 conservative in their decisionmaking.

13 There were four interim analyses that were
14 conducted using the O'Brien-Fleming criteria. These are
15 shown on the right-hand side with the critical values.

16 Additionally, there were four interim analyses
17 conducted for administrative purposes.

18 The columns represent the protocol-specified
19 ways of comparing the arms. Overall tests between the 3
20 curves, using a 2 degree of freedom test, a combined active
21 versus placebo arm, and the two pairwise comparisons of the
22 active arms to placebo.

23 Note that the first three looks at the data
24 were performed using an overall test. A trend was observed

1 in February of 1983 comparing the best arm, which was
2 H/ISDN, to the worst arm, placebo. It was after this
3 analysis that the Operations Committee unblinded
4 themselves.

5 In May of 1983 it is important to note that a
6 significant difference using the O'Brien-Fleming stopping
7 boundary was observed between H/ISDN and placebo. However,
8 the trial continued without change. The majority of the
9 protocol specified comparisons were made after the
10 significant interim result was established, pointed out in
11 this area.

12 Note that even though the overall survival time
13 was used for this analysis, the significant results
14 obtained in May of 1983 were more similar to a 2-year
15 endpoint.

16 The O'Brien-Fleming method was not the pre-
17 specified method in the protocol but was used after the
18 method was published in 1979 as it was easier to implement
19 than the Canner method that was a pre-specified method.

20 The next slide I'm going to show you is not
21 included in the committee packet of slides, nor has it been
22 shared with the FDA, due to the recent completion of this
23 simulation, but we feel it shows strong, supportive
24 information that also assesses the sensitivity of the

1 O'Brien-Fleming method that was used.

2 This slide summarizes the simulation of an
3 interim analysis using the protocol specified Canner
4 method. The results of this simulation support the
5 findings of the O'Brien-Fleming method, indicating a
6 superior mortality benefit for H/ISDN over placebo in May
7 of 1983, as well as in August 1984.

8 The critical p value that was used for this
9 simulation was a .0125 for the comparison of H/ISDN to
10 placebo, a .0125 for Prazosin versus placebo, and .025 for
11 the combined active versus placebo.

12 There were several reasons that the committee
13 did not stop the study after the significant interim
14 finding in May of 1983 was observed. Importantly, the
15 impact of the differences in the baseline characteristics
16 of the patients upon survival had not yet been assessed,
17 and the committee wanted to establish the length of benefit
18 of the H/ISDN effect.

19 In summary, there was a statistically
20 significant interim analysis in May of 1983, according to
21 the O'Brien-Fleming stopping criteria. The study continued
22 beyond May of 1983 to investigate the length of benefit of
23 effect. The protocol-specified secondary analyses -- that
24 is, the Cox model -- were justified based upon the

1 significant interim results. As the May 1983 analysis met
2 the stopping criteria, no penalty is required for the
3 interim analyses that were conducted after this May 1983
4 finding.

5 The next issue is the multiple treatment arm
6 comparisons. As previously shown, the interim testing was
7 conducted in a protected fashion. First, the overall test
8 of the three treatment arms, using a 2 degree of freedom
9 test, was employed. Secondly, the best versus the worst
10 arms were compared in February of 1983, and again in May of
11 1983. Only after a significant result was obtained in May
12 of 1983 were the combined active versus placebo arms and
13 pairwise comparisons made.

14 We would suggest that after significant
15 differences were established in May of 1983, no alpha
16 penalty is warranted for the protocol-planned comparisons
17 performed subsequent to this time.

18 The next issue is the stepwise approach to the
19 analysis, that is, a non-significant log-rank test, then a
20 Cox model analysis. The significant log-rank interim
21 analysis in May of 1983 justified the protocol-specified
22 secondary analysis, the Cox model, without alpha penalty.
23 The analysis of a covariance method gave a more precise
24 estimate of the true treatment effect, especially for

1 overall survival where the estimate of effect is more
2 variable because of the small number of patients in the
3 trial after 3 years.

4 The next issue is the imputation of missing
5 covariate values. There were a total of 459 patients in
6 the placebo and H/ISDN treatment arms in V-HeFT I. There
7 were 51 of 459 patients that were missing either baseline
8 ejection fraction or baseline peak O₂, two of the
9 covariates selected by Dr. Packer as a consultant to FDA.

10 This slide shows the baseline mean values of
11 ejection fraction and max oxygen consumption by survival
12 status. There was a consistent trend independent of
13 treatment group showing that patients dying during the
14 study had a lower baseline EF and lower baseline max O₂
15 than those alive at the end of the study.

16 This slide shows similar data in a slightly
17 different fashion. This slide shows the cumulative
18 mortality by baseline ejection fraction and baseline oxygen
19 consumption during peak exercise. The patients with the
20 lowest ejection fraction and lowest oxygen consumption had
21 the highest mortality during the study.

22 There were incremental advantages in total
23 mortality observed by baseline ejection fraction and oxygen
24 consumption, with patients having the higher baseline

1 ejection fraction and higher baseline oxygen consumption
2 having the lowest mortality.

3 This next slide summarizes a simulation
4 analysis performed by Dr. Jim Hung at FDA, showing
5 alternative methods for imputing missing values of baseline
6 ejection fraction and maximum oxygen consumption. The
7 first row of this table shows the results when the maximum
8 non-missing value is used to impute the missing values for
9 the patients that died, and the minimum non-missing value
10 is used to impute the missing values for the patients that
11 survived. This approach may not make sense, given the data
12 which I have just shown to you, and what we know about the
13 trials regarding the prognostic significance of ejection
14 fraction in oxygen consumption upon survival.

15 The second row shows the results if one uses
16 the mean value to impute the missing values for all
17 patients with missing ejection fraction or max oxygen
18 consumption, regardless if they died during the trial.
19 This is the method that most closely resembles the approach
20 used by Dr. Lloyd Fisher for the analysis submitted in our
21 application. This method leads to a p value of .016 in the
22 Cox model for overall survival and a p value of .013 for 2-
23 year survival.

24 The third row shows the results obtained if one

1 uses the minimum non-missing value for ejection fraction in
2 max O2 as the imputed value for those patients that died
3 during the trial. And the maximum non-missing value of
4 ejection fraction and max O2 for those that did not die
5 during the trial.

6 Based upon the data that I have just shown you,
7 and based upon what we know about the prognostic
8 significance of ejection fraction and oxygen consumption
9 from other trials, this method has strong intuitive appeal.
10 Using this method to impute the missing 51 covariate
11 values, one obtains a p value of .007 for the overall
12 survival, and .01 for the 2-year survival. The true p
13 value probably lies somewhere in between .016 and .007 for
14 the overall survival and probably somewhere between .013
15 and .01 for the 2-year survival.

16 Finally, I would like to point out regarding
17 the last column, labeled log-rank/Cox, these columns
18 indicate the simulation results for the incremental
19 increase in the p value for conducting the Cox analysis
20 after a non-significant log-rank test. As previously
21 mentioned, the statistically significant log-rank test in
22 the May 1983 interim analysis provided a rationale for
23 conducting the Cox analysis without an adjustment in the p
24 value for this approach.

1 In summary, the sensitivity analysis conducted
2 by Dr. Hung indicates a range of nominal p values,
3 depending upon the method used for imputing the missing
4 covariates. Use of a minimum value for deaths and maximum
5 value for survivors is reasonable, given the observed
6 findings and what we know about the prognostic significance
7 of these covariates. Use of a mean value may lead to a
8 more conservative p value, especially for overall survival.

9 The next issue is the two protocol-specified
10 primary endpoints. There was a 33 percent reduction in
11 mortality through 2 years, and a 27 percent reduction in
12 overall study mortality for H/ISDN treated patients. The
13 one-sided 95 percent confidence intervals indicate the
14 H/ISDN risk reduction is consistent with the range of
15 observed findings. The observed risk reduction at both
16 time periods was consistent and correlated, and both
17 findings represent different point estimates of one
18 endpoint, that is, survival.

19 In summary, the consistent risk reduction was
20 observed at 2 years and overall study. The protocol
21 specified a valuation at two time points to assess the
22 length of benefit of effect. The estimate of effect may be
23 influenced by the sample size at 2 years, and at the end of
24 study, and it may be reasonable to consider survival data

1 as one endpoint, having two point estimates of effect for
2 the modest alpha penalty imposed upon the nominal p values.

3 The last issue is the issue of the replication
4 of the study findings. There are three questions that have
5 been suggested by the agency that must be addressed for
6 this issue. Would H/ISDN have beaten placebo if it had
7 been studied in V-HeFT II? And what is an appropriate
8 placebo group to use for this comparison? And is the point
9 estimate of the effect size for H/ISDN less than half the
10 effect size of Enalapril?

11 Because of ethical concerns, the demonstrated
12 mortality benefits observed in V-HeFT I were not
13 replicated. However, the agency has suggested analyses
14 that might be supportive of the mortality benefit and the
15 following is presented as supportive information. We
16 strongly feel that the randomized concurrent control arm of
17 V-HeFT I is the appropriate basis for the mortality
18 benefit.

19 It has been proposed by the agency that the
20 placebo arm from the SOLVD treatment study may be an
21 appropriate arm for comparison. This slide shows the risk
22 ratio for mortality relative to Enalapril for SOLVD
23 treatment, placebo, and V-HeFT II H/ISDN. When the H/ISDN
24 effect is compared to this placebo, there is no observed

1 difference in the risk estimates. This is true at both the
2 2-year and the overall time points.

3 However, this placebo arm is flawed for purpose
4 of making this comparison, of the following reasons. This
5 study allowed the active use of vasodilators and nitrates
6 and the study also allowed open-label use of ACE
7 inhibitors. This placebo arm is therefore not an adequate
8 control for making this comparison. And one would not
9 expect to observe a difference between H/ISDN in such an
10 arm.

11 A more appropriate control arm is the placebo
12 arm from V-HeFT I. The placebo arm from V-HeFT I allowed
13 only digitalis and diuretic use. Once V-HeFT I was
14 completed, it was no longer ethical to use this control arm
15 in this patient population. Use of the V-HeFT I placebo
16 group as a control group for V-HeFT II makes sense, given
17 the similarity of the patient populations studied and the
18 conduct and handling of both trials.

19 As previously shown by Dr. Cohn, this slide
20 shows the survival profile for H/ISDN treated patients in
21 V-HeFT I and V-HeFT II. It is clear that this profile is
22 very similar, but this does not allow one to conclude that
23 the risk reduction for H/ISDN is replicated in V-HeFT II.
24 To do that, one must also consider the data from the second

1 arm of that trial, Enalapril, and how each arm would have
2 performed relative to a placebo group, had there been one.

3 This slide shows the risk reduction and the 95
4 percent confidence intervals for V-HeFT I and V-HeFT II, as
5 well as the risk reduction for Enalapril compared to V-HeFT
6 I placebo, and H/ISDN from V-HeFT II compared to V-HeFT I
7 placebo.

8 It is important to note the following. The
9 risk reduction observed for H/ISDN and V-HeFT I, .73, is
10 consistent with the observed risk reduction for H/ISDN and
11 V-HeFT II, compared to V-HeFT I placebo, .75. There is a
12 strong suggestion of an overall Enalapril benefit in V-HeFT
13 II, even though the 95 percent confidence interval includes
14 1.

15 The risk reduction observed for Enalapril,
16 compared to V-HeFT I placebo, .61, is consistent with the
17 expected conclusion of an Enalapril survival benefit.
18 Importantly, the point estimate of the H/ISDN risk
19 reduction, .75, is not less than half of the point estimate
20 of Enalapril, when both are compared to a common placebo.
21 Also, the upper bound of the Enalapril effect overlaps the
22 point estimate of the H/ISDN effect, as does the lower
23 bound of the H/ISDN effect overlap the point estimate of
24 Enalapril.

1 In summary, V-HeFT I was the only study with a
2 true placebo arm. The Enalapril survival benefit versus
3 V-HeFT I placebo was consistent with the expected survival
4 benefit of Enalapril. The H/ISDN survival benefit from
5 V-HeFT I was replicated in V-HeFT II when compared to the
6 V-HeFT I placebo group, and the point estimate of the
7 V-HeFT II H/ISDN survival effect was not less than half the
8 effect size of Enalapril, when compared to a V-HeFT I
9 placebo.

10 In conclusion, it is reasonable to expect
11 little or no impact upon the nominal p values due to the
12 issues described. The extent of the alpha penalty does not
13 impact the interpretation of the observed survival benefit
14 for H/ISDN in V-HeFT I. And it is reasonable to conclude
15 that the H/ISDN survival benefit was replicated in a second
16 study.

17 And now Dr. Jay Cohn will provide a clinical
18 wrap-up to the presentation.

19 DR. COHN: Well, a number of other endpoints
20 were monitored in V-HeFT I and II and time won't allow us
21 to go into all these, but a few of them have been
22 specifically addressed by the agency, and I'll try to
23 provide those data. In V-HeFT I and V-HeFT II, we measured
24 cardiac hospitalizations as well as we could. Quite a

1 different population because these were VA centers and the
2 criteria for admission to a VA hospital are quite different
3 from those to private hospitals.

4 Quality of life was assessed in both trials,
5 but I must point out to you that in 1979 when we planned
6 V-HeFT I, there were really no appropriate quality of life
7 instruments that could be used, so this was truly not a
8 quality of life assessment. We did use a form in V-HeFT II
9 that I will show you in a moment. It was never validated.
10 It has not been re-used. We have subsequently developed a
11 Minnesota Living with Heart Failure Questionnaire, which
12 was not employed in all the centers in V-HeFT II.

13 We monitored heart size, we monitored
14 echocardiograms. We did Holter monitoring, and we measured
15 plasma norepinephrine levels, and time will not allow me to
16 go into these endpoints.

17 The time to death or hospitalization is shown
18 here because the agency asked about hospitalizations. This
19 is the V-HeFT I data showing time to death or
20 hospitalization, and you can see there was a clear trend
21 for the H/ISDN group to fare better than the placebo group,
22 but this was not statistically significant.

23 This is the analysis of the V-HeFT II, that is,
24 time to death or hospitalization. In V-HeFT II, and as you

1 might predict, there was a more favorable effect of
2 Enalapril compared to H/ISDN, largely reflecting the
3 mortality difference because when we look at just the time
4 to first hospitalization for any reason in V-HeFT II, the
5 two curves for Enalapril and H/ISDN superimpose and there
6 is no difference at all between them.

7 If one accepts, then, that Enalapril has a
8 significant impact on hospitalizations and reduces it, as
9 it has in other studies, one might conclude that H/ISDN is
10 not different from Enalapril in that regard.

11 This is the quality of life assessment we did
12 in V-HeFT II, called a Heart Condition Assessment Score.
13 This is the changes over time, an increase being an
14 improvement in quality of life, a decrease being a decrease
15 in quality of life, and there is no striking difference
16 between H/ISDN and Enalapril.

17 At the first time point, 3 months, where the
18 agency has almost all of its data on quality of life in
19 heart failure and the effects of therapy, H/ISDN exhibited
20 a significant increase. Enalapril did not. That p value
21 was less than .05 at 3 months.

22 Thereafter, quality of life declined
23 progressively in both groups, which tells you a little bit
24 about the natural history of heart failure. At all time

1 points, though, there was a greater decline in quality of
2 life in the Enalapril group than in the H/ISDN group,
3 suggesting a trend for more favorable effect of H/ISDN,
4 consistent with the trends on exercise performance.

5 Now, the safety of these two drugs I won't go
6 into. You have it in your document, all the side effect
7 data. The safety has been well characterized. We know,
8 and it has been confirmed, that H/ISDN causes headache and
9 that is reduced when the dose is reduced. We know that
10 Enalapril causes cough and that clearly appeared in the
11 database.

12 There were essentially no instances of lupus in
13 V-HeFT I. There were two possible cases in V-HeFT II, but
14 it's clear that the incidence of lupus as a complication of
15 hydralazine is exceedingly uncommon in this patient
16 population.

17 Now, the issue of nitrate tolerance has been
18 raised repeatedly, both in the clinical arena and by the
19 agency because of the well-known tolerance that develops to
20 continuous nitrate administration in their treatment of
21 angina. The mechanisms for this nitrate tolerance have in
22 the past not been clarified. There are many mechanisms
23 that have been suggested, but there is recent and perhaps
24 the most exciting data of all, the role of hydralazine as

1 an inhibitor of nitrate tolerance.

2 It appears that when we serendipitously put
3 these two drugs together in the late 1970s, not knowing at
4 all what the interaction was but knowing that they were
5 both vasodilators, we did something that proved to be
6 remarkably effective, and that is, we added to nitrate a
7 nitrate tolerance inhibitor. I'll show you just briefly
8 the data on that issue.

9 It has been well established in a number of
10 laboratories, laboratories of Munzel and Harrison and
11 Besange, that nitrate tolerance is associated with the
12 generation of superoxides at the endothelial surface.
13 These superoxides chew up nitric oxide and thus inhibit the
14 nitric oxide effect which characterizes the hemodynamic
15 response to nitrates.

16 This is just one slide from a paper by Winslow
17 that was published in the Journal of Clinical Investigation
18 last year, in which superoxides are measured in response to
19 NADH addition as a substrate. This is carried out in
20 ground-up aortas from rabbits, who were either not treated
21 with nitroglycerin or treated with nitroglycerin, or
22 treated with nitroglycerin in addition to hydralazine for 3
23 days before the aortas were taken out and ground up.

24 You will notice that this is the superoxide

1 production in response to NADH in a controlled animal that
2 received neither nitroglycerin or hydralazine. This second
3 black bar is the increase that is identified when the
4 animal had been treated for 3 days with nitroglycerin, an
5 excess by about two or three-fold of the amount of
6 superoxide that is produced in the vasculature.

7 When hydralazine was added to nitroglycerin in
8 the treatment of these animals for 3 days, there was no
9 excess of superoxide produced, implying that the
10 hydralazine had prevented the generation of the superoxide
11 which causes nitrate tolerance.

12 Now, the in vivo documentation of this
13 combination has been well established. This is a study
14 performed by Dr. Ho-Leung Fung, who is in the audience in
15 case there are any questions raised about this, in which he
16 took rats with myocardial infarction who had an elevated
17 left ventricular end diastolic pressure and infused
18 nitroglycerin continuously.

19 In open circles is the response of the left
20 ventricular end diastolic pressure to nitroglycerin. It
21 comes down and then gradually recovers, despite the fact
22 that the nitroglycerin infusion is continued. This
23 recovery to pre-treatment levels implies nitroglycerin
24 tolerance, the hemodynamic effect of the nitroglycerin.

1 When in fact he added hydralazine to the
2 regimen, which in itself did not change LVEDP, the fall was
3 comparable with the nitroglycerin but now the nitroglycerin
4 effect was sustained over 10 hours. This is a significant
5 inhibition of the tolerance that developed in the
6 nitroglycerin-alone treated rats.

7 And then to bring this to the clinic, Dr. Uri
8 Elkayam and his colleagues in Los Angeles -- and Uri is
9 also in the audience in case there are any questions -- did
10 the same trial in humans with heart failure. Infusion of
11 nitroglycerin in these patients with heart failure produced
12 a decline in the pulmonary capillary wedge pressure and
13 then when the nitroglycerin infusion was continued, the
14 wedge pressure rose progressively, implying tolerance to
15 the hemodynamic effects of nitroglycerin.

16 When hydralazine was co-administered with the
17 nitroglycerin, the favorable effect of nitroglycerin on
18 pulmonary-capillary pressure was sustained. So, there
19 appears to be rather persuasive evidence now that
20 hydralazine is a potent antioxidant which inhibits the
21 tolerance that may develop to nitroglycerin or to
22 isosorbide dinitrate.

23 Now, I am not willing to accede that
24 hemodynamic tolerance is necessarily also implied, that

1 there is tolerance to the anti-remodeling effect of
2 nitrates on left ventricular function. I think these must
3 be viewed as separate endpoints, and we can't assume that
4 one is related to the other. But I think that this is
5 clear evidence that whatever tolerance might develop during
6 chronic administration of isosorbide dinitrate should very
7 much be inhibited by the co-administration of hydralazine.

8 Well, I alluded at the beginning to the fact
9 that the guideline committees have approved this therapy
10 already and I just remind you, and you have in your
11 briefing document the details of these guidelines, and in
12 fact many members of this committee have served on these
13 guideline committees. There are three identified here.
14 That is, the guidelines issued by the American College of
15 Cardiology and the American Heart Association for the
16 treatment of heart failure, the guidelines issued by the
17 Agency for Health Care Policy Research, and the guidelines
18 for heart failure treatment issued by the World Health
19 Organization.

20 All of these guidelines recommend for therapy
21 of heart failure digoxin and diuretics, the use of ACE
22 inhibitors, and the use of hydralazine and isosorbide
23 dinitrate in patients who are not taking an ACE inhibitor.
24 They do not suggest this should replace ACE inhibitors,

1 that this should be used in patients who do not take those
2 drugs.

3 Well, I just would like to finish up by putting
4 in context what I have learned from these V-HeFT trials
5 because this has changed the paradigm. We used to think
6 that heart failure was a syndrome in which there were many
7 endpoints, all of which should be in concert. I think we
8 now know that they are distinct, and that the progressive
9 process in the left ventricle with dilatation, which we
10 call remodeling, and a progressive fall in ejection
11 fraction leads to premature death from arrhythmias or pump
12 failure, and this process may continue and progress to
13 death in the absence of symptoms.

14 In fact, the SOLVD trial, the SOLVD prevention
15 trial, was initiated to identify patients out here with a
16 low EF and no symptoms. So that it is quite possible to go
17 through this whole disease without symptoms. The presence
18 of symptoms relates largely to noncardiac factors which may
19 be variably stimulated by this process in the left
20 ventricle, and may include neurohormonal activation and
21 multiple other factors as well.

22 Most of the data that have been previously
23 reviewed by the FDA for treatment of heart failure for
24 relief of symptoms have involved short-term studies in

1 which symptom relief is really a short-term goal of
2 therapy. In contrast, if one is interested in this process
3 leading to death, one must do a long-term trial and one
4 must use therapies to interfere with this process that may
5 be quite separate from therapies aimed at relieving
6 symptoms.

7 So, I currently view the management of heart
8 failure really with two different goals in mind. One is
9 short-term symptom relief, and for that we often use -- we
10 do use -- diuretics and vasodilator may favorably affect
11 short-term symptoms by producing a favorable hemodynamic
12 effect. And we even use occasionally positively inotropic
13 drugs like dobutamine and milrinone in order to have a
14 favorable effect on hemodynamics and on symptoms, despite
15 the fact that we know that these drugs shorten life
16 expectancy, apparently, and some of these drugs have no
17 effect on life expectancy and some may shorten it. So that
18 there is no relationship between the favorable effect of
19 these drugs on symptoms and the potential for therapy to
20 alter the long-term course of the disease.

21 From what we now know, progressive left
22 ventricular dysfunction can be inhibited and therefore
23 mortality reduced by ACE inhibitors, by hydralazine and
24 isosorbide dinitrate, I believe by beta-blockers -- and you

1 are going to be dealing with that contentious issue this
2 afternoon -- and perhaps by other neurohormonal inhibitors
3 which can alter the milieu and influence the rate at which
4 the left ventricle remodels, yet to be determined out here.

5 But I think we have reached the point now where
6 we have to identify specific endpoints for a therapeutic
7 approach. The only agent which appears on both sides of
8 these columns is hydralazine and isosorbide dinitrate
9 because it does relieve symptoms and improves exercise as a
10 potent vasodilator, and it also inhibits the progressive
11 remodeling process in the left ventricle.

12 Well, in summary, then, I hope we have been
13 able to convince you, Mr. Chairman, that there is a strong
14 basis for approval of BiDil for congestive heart failure.
15 That is, that the combination of hydralazine and isosorbide
16 dinitrate exhibits a survival benefit compared to placebo;
17 that it exhibits a strong trend for improved exercise
18 tolerance versus both placebo and versus Enalapril and
19 V-HeFT II; that it produces a sustained improvement in
20 ejection fraction, which I believe means that it is
21 inhibiting the remodeling process and it also confirms the
22 long-term effect of these two vasodilators; that this
23 combination therapy has a well-established rationale, even
24 more well-established by the recent data relating to

1 nitrate tolerance; that the safety of this combination is
2 well-established; that it is already widely recommended as
3 a treatment option in all the guidelines issued for the
4 management of heart failure; and that indeed the practicing
5 physicians require prescribing information to properly
6 utilize this remarkably effective therapy.

7 Thank you very much.

8 DR. MASSIE: Thank you very much, Jay.

9 The way I think we should proceed from here is
10 first open up this presentation to questions from the
11 committee and our consultants. We are going to lead off
12 with our reviewers, as we usually do, and our consultants,
13 and if the reviewers from the FDA want to ask some
14 questions at that point, that would also be appropriate.
15 Then we'll ask the reviewers from the FDA for comments and
16 then we'll proceed on to the questions.

17 So, why don't we start. Lem, do you want to
18 start, since you had some statistical questions?

19 DR. MOYE: Sure.

20 In nowhere as part of the slide presentation
21 that we saw today did I see the -- and if this was here and
22 I missed it, I apologize, but I don't think I saw the log-
23 rank analyses which led to the p value of 0.093. And I
24 wondered if you could comment on that.

1 DR. QUINN: I think you are referring to the
2 two-sided log-rank test that was in the original
3 application?

4 DR. MOYE: That's right.

5 DR. QUINN: Well, that has been presented as
6 the one-sided p value that corresponds to that two-sided
7 test, as the protocol specified the one-sided p value as
8 the appropriate method.

9 DR. MOYE: And so the one-sided p value is what
10 precisely?

11 DR. QUINN: Can I go back to that slide?

12 It would be the one from Dr. Cohn's presentation of
13 the summary of the V-HeFT I survival.

14 DR. MOYE: That's where I think I first asked
15 the question. It's 0.04.

16 DR. COHN: It's .046, I think.

17 DR. MOYE: Okay.

18 Now, the threshold for significance, which was
19 prospectively specified by the investigators, was at, again
20 one-sided, 0.025. Is that right?

21 DR. QUINN: Well, it's difficult to interpret
22 the protocol actually. The protocol suggested that
23 different alternatives could be employed, depending upon
24 the number of comparisons that were made. And the protocol

1 suggests that if the combined active versus placebo arm was
2 compared, as well as the two individual active arms to
3 placebo, then that the individual active arms to placebo
4 could be compared at the .0125.

5 However, the protocol doesn't necessarily lead
6 one to believe that all those tests would be conducted and
7 the pairwise comparisons could also have been tested at
8 .025 and the rationale that I'm trying to make is that the
9 interim analysis of May 1983 that met the O'Brien-Fleming
10 stopping criteria, was the significant log-rank test found
11 for the trial.

12 DR. MOYE: But since the trial was allowed to
13 continue, I think it's also admissible that that might not
14 be the definitive p value because of course, as you get
15 these multiple p values, as you go through the interim
16 analyses, one could choose any p value they wanted and
17 continue to go through the trial, amassing additional p
18 value. There is a problem with that approach, right?
19 Okay.

20 One other question. The protocol is actually
21 quite laudatory of the log-rank test. I will not read the
22 individual statements from the protocol, but there are I
23 think two locations where they mention the superiority of
24 the log-rank test and that it is distribution-free, and I

1 think they go so far as to say that one of the best tests
2 available to identify small differences between treatments
3 is the log-rank test.

4 Yet, now there is a good deal of emphasis on
5 the Cox analysis approach. I could only find one brief
6 mention of the Cox analysis approach in the protocol and if
7 I compared statements about the log-rank versus statements
8 about the Cox, my view would be that the investigators were
9 hanging their hopes on the log-rank and not the Cox. Yet,
10 we see a good deal of analyses today centered on the Cox
11 progression analysis approach.

12 DR. QUINN: Well, the survival curves become
13 more variable at later time points of the trial, and the
14 Cox model helps to partition out some of that variability
15 and to assess the treatment effect.

16 DR. COHN: Yes, if I could just comment about
17 that, Dr. Moye, because you have to remember, this protocol
18 was planned in 1978 or 1979. There were no data yet on
19 long-term follow-up of heart failure. So, the possible
20 potency of covariates and variables in influencing
21 mortality was completely unknown at that time.

22 I think that all current trials in heart
23 failure are done recognizing those variables and adjusting
24 for them, usually with a Cox analysis.

1 I agree with you. At the time this protocol
2 was written, the Cox analysis was not necessarily
3 identified as an important determinant, for the very reason
4 that we were not very cognizant of how important these were
5 going to be in influencing this ultimate survival.

6 DR. MOYE: So, I guess the crux of the matter
7 here for me is, is there ever a circumstance when the
8 primary statistical prospectively stated analysis plan can
9 be adumbrated, can be substituted by another analysis plan
10 using another stat analysis procedure?

11 DR. COHN: Again, I think you are entirely
12 right, and that is why we have gone into this intensive
13 analysis of the statistics because that question has come
14 up repeatedly and we can only show you the data as they
15 are. These are the p values. One has to interpret them as
16 one chooses to do.

17 But keep in mind that this is a study designed
18 20 years ago. This was a VA cooperative study. This was
19 not designed really as a regulatory study so that careful
20 selection of criteria for endpoint were not as precise as
21 one would see in a protocol designed today with the goal to
22 come to this committee and ask for approval. So, one has
23 to look at this a little differently than one might at a
24 more recently organized mega-trial in which p values are

1 clearly defined as the goals for the trial.

2 DR. MOYE: Thank you.

3 DR. MASSIE: Let me just read the statement I
4 think that Dr. Moye was pointing out. This is in the
5 analysis method of the protocol, the PF1 on page 34, where
6 it said that variables which are prognostically important
7 will be identified by comparing survival curves of patients
8 on different levels of baseline variables. The life table
9 regression procedures of Cox will also be used to identify
10 variables that are prognostically important and to obtain
11 estimates of treatment effects adjusted for any equality in
12 their distribution between treatments.

13 Now, one thing that struck me on the baseline
14 characteristics is there were no inequalities of those
15 prognostically important variables. Was that the case?

16 DR. COHN: Yes. There were no significant
17 differences when one asks are there differences between the
18 two groups, but of course there are subtle differences
19 which may impact upon mortality that don't reach
20 statistical significance when one compares the two groups.
21 It has been the usual approach in V-HeFT to look at all
22 variables and not just confine oneself to variables that
23 show a significant difference between the two treatment
24 arms.

1 And you can see the degree of adjustment that
2 was required when we switched from a log-rank test to a Cox
3 analysis, albeit using now only those variables identified
4 by the agency and not the variables that we had originally
5 planned on using because they were preselected
6 independently.

7 DR. MASSIE: It's just that in my naivete I was
8 surprised that there was such a substantial difference in
9 the outcome of those analyses, despite the lack of what
10 looked like even trends. I saw a .5 difference in VO2, but
11 everything else looked right-on. I wondered how much of
12 that might have been as a result of imputation of the
13 missing values as opposed to --

14 DR. COHN: Well, there were only 51 missing
15 values in this whole group out of --

16 DR. QUINN: 459.

17 DR. COHN: -- 400 and some patients, so it's
18 really a relatively small number.

19 It would probably be appropriate -- Lloyd, do
20 you want to make a comment about that? Because Lloyd has
21 really spent a lot of time going over these data.

22 DR. FISHER: Well, just that the reason you can
23 get a difference is, there are papers out showing in the
24 Cox model, if the Cox model with covariates holds, if it is

1 appropriate -- and that is an if -- then if you leave out
2 other covariates, you bias the estimated effect downward.
3 That is, I think, Piantadosi and Sam Weyend and some other
4 people have published that.

5 So, perhaps the reason there is a change is
6 slightly analogous to in the analysis of variance you can
7 reduce your variability by taking into account factors. It
8 is not that you are correcting for baseline imbalance, but
9 you have a more precise treatment estimate when you also
10 take into account the other factors, and that does not
11 contribute to the variability. That would be my guess that
12 that is how this happens.

13 Now, having said that, how you would actually
14 prove a statement like that I am not sure, but it certainly
15 can happen mathematically.

16 DR. MASSIE: Lem, and then I thought I would
17 ask Dr. D'Agostino to comment after Lem.

18 DR. MOYE: Just one brief question. I wonder
19 if you would comment on the concerns that have been raised
20 about the lack of fit of the Cox progression model.

21 DR. FISHER: Pardon me. About the lack of fit?

22 DR. MOYE: The difficulty with the
23 believability of the underlying assumptions required by the
24 Cox regression model.

1 DR. FISHER: Yes, I would be happy to comment
2 on that because that's actually how I got involved in this.

3 Things were somewhat down the road and the FDA
4 review said the fit was examined in two ways, minus log
5 plots. And also on the SAS output there was a statistic
6 for fit. One of the p values for goodness of fit was .049
7 or something.

8 And I came in there and I looked at the plots
9 and I said, hey, this is proportional hazards. I knew
10 that. I mean, I looked at it. Now, this isn't proof, this
11 is Gestalt.

12 So, what I suggested to the agency, I said,
13 let's go to the randomization test. We'll use the Cox
14 statistic but because we're worried about the parametric
15 assumptions, we will go to the randomization test for the
16 treatment effect, which is what we did, the primary thing
17 actually that I did in my analysis.

18 Before that was done that was agreed upon at a
19 meeting with the agency that -- of course, the
20 randomization test is always valid. It doesn't depend on
21 the assumptions. The p value actually turned out to be
22 almost exactly the same. To be perfectly frank, even
23 before we did it, I knew that would happen because I had
24 seen the plots and it looked like proportional hazards.

1 But nevertheless, I think it will alleviate
2 that concern with the agency. I assume that Jim is here,
3 and if the agency still has concerns about that, they can
4 bring them up. I don't think that's much of an issue here.

5 DR. MASSIE: Ralph, do you want to help?

6 DR. D'AGOSTINO: Well, I'm not going to help
7 but I'm going to say something.

8 I guess I'm not overwhelmed with the notion
9 that the protocol says a log-rank test as the major test,
10 and then later on one may want to shift to a Cox. I have
11 written protocols where the analysis that we actually used
12 wasn't even invented when the protocol was being written.
13 So, the notion of shifting is not too dramatic.

14 But in this case here there is such a heavy
15 reliance on the log-rank test that you sort of say that
16 this is the procedure to be used, and then when they're
17 shifting to the Cox, as the analysis is produced, it does
18 become bothersome in terms of trying to sort out, is it
19 chasing after something that's going to show significance,
20 or is it something that you really believe is the best
21 method.

22 The other point that really bothers me is that
23 I can't sort out what the primary variables are. It seems
24 to me like there are a lot of primary variables, which

1 means that there is a lot of testing that is going to go
2 on. And now it looks like there is only a couple of
3 primary variables, which means maybe there shouldn't be too
4 much adjusting.

5 Could someone really clarify? I thought I
6 heard a presentation that there were a lot of secondary
7 variables, but in the materials I had, there were something
8 like six primary variables. That would lead you to say
9 that you committed to those variables.

10 DR. COHN: The protocol did have, I think, six
11 variables as primary endpoints. I know if I were rewriting
12 the protocol today -- and I can't do that -- and we had in
13 mind a regulatory consideration, we would have more
14 precisely defined what were primary and what were
15 secondary. In 1979, that was not done.

16 We all knew as we were progressing -- and we
17 certainly have learned since then -- that the important
18 variables are the ones that I focused on this morning
19 because we now know those are the important variables in
20 heart failure.

21 How did we learn that? We learned that from
22 V-HeFT. So, this is a self-fulfilling prophecy. You do
23 the study, you learn about the disease by doing the study,
24 and then it would be nice to then go back and redesign your

1 protocol, but we don't have the luxury to do that.

2 So, what you are saying is correct. One has to
3 recognize there were a number of variables.

4 The beauty, of course, of this is that every
5 variable went in the same direction. So, we haven't hidden
6 anything. I have alluded to some of those. The trends
7 were all favorable in everything that we looked at. I hope
8 that gives some comfort to the agency in the approval of
9 the drug because there really is consistency across all the
10 variables.

11 DR. D'AGOSTINO: One of the concerns that I
12 think we might have with that is that you then really use
13 the study in an exploratory fashion, which is we learn from
14 studies. But it still then leaves us with the sense that,
15 do we believe the way the variables ultimately were sorted
16 out would, in fact, be confirmed in yet another trial. I
17 think this is where my problems come from.

18 DR. COHN: We have what we believe is strong
19 support for the other variables in V-HeFT II. So, you have
20 seen two trials in which the second -- the other endpoints
21 all went in the same direction, and I think that should
22 give you confidence that V-HeFT I has been replicated.

23 DR. MASSIE: JoAnn?

24 DR. LINDENFELD: Dr. Cohn, I have some concerns

1 about dosing intervals. V-HeFT I and V-HeFT II were both
2 q.i.d., and I understand the approval is for t.i.d., or is
3 it for q.i.d.?

4 DR. COHN: No, the approval should be for
5 q.i.d. The data are q.i.d.

6 DR. LINDENFELD: All right, good.

7 DR. COHN: I think some of the recommendations,
8 at least in one of the guidelines, is for t.i.d., based
9 upon intuition, certainly not based upon data, and we are
10 here with data, not intuition.

11 DR. LINDENFELD: Good.

12 DR. MASSIE: I'm just going to go to our
13 consultants first and then we will open it up to the whole
14 committee. Bob and Jim, any comments, questions?

15 DR. CODY: A couple of questions. Did any
16 patients who participated in V-HeFT I participate in V-HeFT
17 II? How many would you say, what percentage?

18 DR. COHN: Yes. I think about 15 to 20 percent
19 of V-HeFT I patients who survived V-HeFT I were recycled
20 and re-randomized into V-HeFT II. This of course is a
21 major reason why we have never merged these two databases
22 because of the overlap of patients.

23 We have done extensive analysis to see whether
24 there was any difference in behavior of those patients who

1 were re-randomized as compared to those new patients
2 entered into V-HeFT II, and there appeared to be no
3 interaction whatsoever. So, we feel comfortable that they
4 can be treated as if they were the same subset -- from the
5 same set of the population, but that does influence a
6 couple of things in terms of age, for instance. They
7 already were a few years older.

8 DR. CODY: In terms of the very sophisticated
9 statistical analyses that have been done and presented
10 today, has this been factored in, or does it need to be
11 factored in? I would have to defer that to people who know
12 a lot more about statistics than I do.

13 DR. QUINN: Actually I can answer that
14 question, that the results were done both ways for V-HeFT
15 II, both using all the patients that were randomized to
16 that trial, as well as looking at the patients that had not
17 been in the V-HeFT I study. The results were absolutely
18 consistent using both methods.

19 DR. CODY: What percentage of the patients in
20 V-HeFT I and II were women?

21 DR. QUINN: There were no women in the trial.
22 It was all conducted in the VA hospital setting.

23 DR. CODY: I raise this because of the current
24 VA and NIH push to include women in heart failure trials in

1 a more representative fashion. This is certainly an issue
2 with at least one of the VA-sponsored heart failure trials
3 that are currently underway.

4 We are assuming that we could extrapolate these
5 findings across genders. Is that a reasonable assumption?

6 DR. COHN: Well, I guess your assumption, Jeff,
7 is as good as mine. Certainly when one has looked at the
8 response in women versus men in the trials where both
9 groups have been included, such as the SOLVD trial, there
10 appeared to be no difference in the therapeutic response.

11 Women were not included in V-HeFT because we
12 recognized we would have so few that it would not be
13 possible to analyze them separately, so we confined the
14 study to males. The extrapolation to the female population
15 then is going to be a matter of judgment rather than of
16 data.

17 DR. CODY: I guess a final comment is, I think
18 a very important statement that has been made by the
19 presenters, and that is the need for prescribing
20 information for this combination. What data exists to
21 suggest or to guide people when to use BiDil instead of an
22 ACE inhibitor? When do you use BiDil in addition to an ACE
23 inhibitor, and can these findings of functional class 2 and
24 3 patients be extrapolated to functional class 4.

1 DR. COHN: Your last comment is a very
2 important one, and since there was an exercise entrance
3 criteria in all of these patients, class 4 patients were
4 substantially eliminated from the trial. There were a
5 smattering of patients who were said to be in class 4
6 failure, and as you know, a patient might have been in
7 class 4 failure last month and now is ambulatory and
8 functional and gets included in the trial. Is he now a
9 class 4 or is he a class 3? We argue about that all the
10 time.

11 But there really is little data in class 4
12 patients in this trial. There is a good deal of experience
13 with the combination therapy clinically on hemodynamics in
14 class 4 failure, but they were not included in this trial.

15 I think your first issue was --

16 DR. CODY: Using BiDil instead of an ACE
17 inhibitor or in addition to?

18 DR. COHN: Yes, the place of this in therapy.
19 Obviously, the labeling that is being requested would point
20 this out as alternative therapy to an ACE inhibitor in
21 patients who were not receiving an ACE inhibitor usually
22 because of intolerance or perceived intolerance. We know
23 that the analyses done of the use of ACE inhibitors in
24 patients with heart failure continues to suggest that there

1 is a large number of patients not receiving an ACE
2 inhibitor who, on the basis of the data, should be
3 receiving an ACE inhibitor. So, this would be alternative
4 therapy for that group of patients who physicians choose
5 not to use an ACE inhibitor.

6 We are providing no data on this combination
7 added to an ACE inhibitor, and we would not anticipate that
8 that should be included in the labeling. Many of us in
9 clinical practice use that combination because we have
10 found anecdotally that it is effective. But there have
11 been no systematic studies done of hydralazine-isosorbide
12 dinitrate added to an ACE inhibitor to justify that as a
13 labeling indication.

14 DR. CODY: I agree with you that that there are
15 patients where we would use the combination, and generally
16 those would be the patients who aren't doing well. They
17 might be the functional class 4 patients who are not
18 responding to an ACE inhibitor or the hydralazine nitrates,
19 so we combine them. Where clinically, where this piling on
20 concept is used for the sickest patients, do we have to
21 have some special wording or recommendations about that?

22 DR. COHN: Yes, I agree with you completely,
23 Bob. That is really the way we have to focus this therapy
24 based upon the data from V-HeFT. We have to limit the

1 indication to what has been demonstrated in V-HeFT. I
2 appreciate your comments, Bob.

3 DR. MASSIE: Just one qualification and then
4 Ray has a question.

5 When you say in people who are not using ACE
6 inhibitors, would it make more sense in people who have
7 been tried on ACE inhibitors and have not tolerated them?
8 In order to best serve the educational function that what
9 we are trying to do is get people to use ACE inhibitors and
10 we know there are people in whom you can't, but not just in
11 people who are not on them because that would be any heart
12 failure patient who is newly diagnosed and hasn't yet had a
13 chance to be treated.

14 DR. COHN: Well, you know, you may be right.
15 On the other hand, if you look at the ancillary endpoints
16 such as exercise, and one had a therapeutic goal in an
17 individual in whom prolongation of life, based on whatever
18 other issues might be present in that individual, was not
19 your primary emphasis, and your primary emphasis was to
20 allow the patient to do a little more exercise, one might
21 conceivably feel that in that instance the mortality
22 benefit of Enalapril was not important to this patient.

23 Now, these are judgmental issues that
24 physicians have to cope with, so it is difficult to demand

1 that all physicians give all patients with heart failure an
2 ACE inhibitor. It is important to show them the benefit of
3 ACE inhibitors so that they can choose to use those drugs
4 in the appropriate patient population. So, it is a very
5 nebulous kind of distinction, but I think physicians have
6 to be given choices.

7 DR. MASSIE: Ray?

8 DR. LIPICKY: I have forgotten the operant
9 policy during the studies with respect to how the dose was
10 manipulated with respect --

11 DR. MASSIE: Can you speak a little louder,
12 please?

13 DR. LIPICKY: Sorry. I have forgotten the
14 operant policy with respect to how dose was manipulated
15 during the studies. Was it titrate to maximum tolerated
16 dose with some upper limit?

17 DR. COHN: Yes. The upper limit was 40
18 milligrams 4 times a day of isosorbide dinitrate, and 75
19 milligrams 4 times a day of hydralazine. It was a dual
20 titration, and that is, both drugs were increased at
21 subsequent visits until the patient achieved that higher
22 dose.

23 If headache, which was the major side effect,
24 intervened, the dose could be either held or even reduced,

1 and that is why the mean dose in V-HeFT I was about 240
2 milligrams of hydralazine, not 300, and the mean dose of
3 isosorbide dinitrate was about 110 milligrams and not 160
4 milligrams reflecting that.

5 DR. LIPICKY: But dose was increased for both.

6 DR. COHN: For both.

7 DR. LIPICKY: They were not changed
8 independently.

9 DR. COHN: No. Although if a side effect
10 occurred, the physicians were encouraged to reduce the dose
11 of the ISDN first because it was our impression that that
12 was the more likely cause of headache. So, they might have
13 reduced one and not the other. And sometimes they
14 discontinued one and not the other.

15 Now, we had a little trouble dealing with that
16 discontinuation of one of the drugs because they were
17 taking one and they weren't taking two. Knowing what we
18 know now, it's possible you need to take both in order to
19 get the beneficial effect. But it was all an intent-to-
20 treat analysis anyway, so that analysis was not influenced
21 by whether they did or didn't take both drugs.

22 DR. LIPICKY: From the vantage point of
23 instructions for use, and based on the experience, do you
24 think it's a problem that one has to take both and does not

1 have a choice in titrating one or the other, depending on
2 adverse symptoms?

3 DR. COHN: I think our data would suggest that
4 if one wants to attain the benefit of this drug
5 combination, one should use the two drugs. We have no way
6 of analyzing what the optimal dose of each of those two
7 combinations is, as you know, and this was not a dose
8 response study. So, we are left with a strategy for
9 therapy, a strategy for reducing the dose if side effects
10 occurred, and when one used that strategy, we reduce
11 mortality.

12 Now, I think from a labeling standpoint, all we
13 can do is recommend that strategy in the labeling, knowing
14 full well that that may not be the optimal strategy or the
15 only strategy, but the only strategy we studied.

16 DR. MASSIE: Ray, while you have the
17 microphone, before we open the general discussion, maybe we
18 can get you to clarify something for us. The idea of a
19 combination drug as opposed to the two components of the
20 drug. I think you started hinting on that point a bit.

21 What would the FDA see as a reason for
22 approving a combination drug when we have the two
23 components, and I guess then I would like Jay to follow up
24 and tell us why he thinks it is better to have this

1 combination rather than the two components, what advantage
2 it provides, because ordinarily I know in combination drugs
3 where we have dealt with them for hypertension, you have to
4 show both components are effective and then there is some
5 advantage to having the two together. Maybe, Ray, you
6 could tell us why we should be thinking about this.

7 DR. LIPICKY: It could be a very long
8 discussion but I think the short discussion is that if one
9 has a trial where one thinks there has been documentation
10 of an alteration in irreversible harm, and one knew that,
11 say, it was a single chemical entity, but it was a
12 racemate, nobody would have any problems whatsoever in
13 saying that the drug, a racemate, did it.

14 I think that if you consider this to have been
15 documented, to have an effect on something that is
16 irreversible, well, then you are stuck, or not stuck. It
17 is appropriate to consider the combination as a single
18 drug.

19 Ordinarily one would expect to be able to
20 document that drug A plus drug B has a bigger effect than
21 either drug A or drug B alone at the appropriate doses.
22 But ordinarily one would be concerned about that if one
23 could in fact do studies that would allow one to determine
24 that. It is unlikely to be able to do them for

1 irreversible harm, especially with a study that is 20 years
2 old.

3 DR. TEMPLE: Barry?

4 DR. MASSIE: Can I just let Jay respond?

5 DR. TEMPLE: Barry? I'd like to add something.

6 DR. MASSIE: Go ahead.

7 DR. TEMPLE: We have a combination policy that
8 doesn't distinguish really between taking the two drugs
9 separately and putting them in the same tablet. That is
10 theoretically of no concern. It is never a benefit to have
11 them in one tablet except convenience. There can't be a
12 medical benefit from taking them together as both
13 separately. The question is, do they each contribute, as
14 Ray said. The longstanding policy is you have to
15 demonstrate that each component makes a contribution.

16 We have, however, tried to confront the
17 question of, suppose somebody shows you that you've done
18 something important with two drugs and it is really not
19 possible anymore to test the two components because you
20 can't have the placebo group to do it.

21 What we have said is, if there is a plausible
22 basis for having both components, on theoretical grounds we
23 would sort of live with the discomfort of approving the
24 combination if it had an important effect on survival or

1 irreversible morbidity or something like that.

2 DR. COHN: I think the answer to your question,
3 Barry, is a complicated one. Let me put it this way.

4 If one looks at the use of this drug
5 combination in its generic form, out in the community,
6 there is very little use of hydralazine. There is
7 substantial use of nitrates. ISDN is widely employed in
8 heart failure, without labeling, and without indication and
9 without marketing.

10 Hydralazine is not used, perhaps for several
11 reasons. Number one, physicians don't like writing so many
12 prescriptions because they would have to write two separate
13 prescriptions. Patients do not like taking so many pills.
14 And there is no dosage form available of hydralazine which
15 matches the dosage form used in V-HeFT. So, there are
16 several impediments to the use of hydralazine.

17 The nitrate use suggests that physicians are
18 very comfortable using ISDN because they are comfortable
19 with that drug. And they are using it for reasons which
20 are mysterious because there is no existing database which
21 suggests that ISDN should be used in patients with heart
22 failure, other than the V-HeFT database, which we now
23 believe strongly suggests, based upon the new data that I
24 showed you, that hydralazine should be used along with

1 ISDN.

2 So, having labeling for BiDil, if it will help
3 physicians to understand the application, the dosing and
4 the usefulness of these two drugs and can do it in a single
5 prescription, with a single tablet that patients will be
6 much more comfortable taking, I think it can have a
7 profoundly favorable effect on the management of this
8 syndrome because, despite the fact that all the guideline
9 committees recommend using this combination, it is not
10 being used.

11 There has to be some explanation for that, and
12 that's the best explanation I have, is what I have given
13 you.

14 DR. MASSIE: Okay. Well, what we are going to
15 do is, Jeff, since he has not gone, and then we will start
16 from the right.

17 DR. BORER: Most of the questions I had have
18 been answered, but I need a clarification here, if I can
19 have one, please, and then based on the response to that I
20 have several questions I would like to pose.

21 First of all, I would like a clear statement of
22 what is being requested for approval here. What is the
23 indication? Are we talking about approving the combination
24 for reducing mortality rate in patients with congestive

1 heart failure, or are we being asked for approval of the
2 combination for the treatment in general of people with
3 heart failure because at least three things look like they
4 get better, mortality rate and maybe exercise tolerance and
5 maybe ejection fraction?

6 What indication is the sponsor seeking here in
7 the approval process?

8 DR. COHN: Well, I guess if you are speaking of
9 the sponsor, maybe we should turn to the sponsor. Cesare,
10 do you want to respond to that as the sponsor?

11 DR. ORLANDI: The indication that we are
12 pursuing is for treatment of congestive heart failure in
13 addition to digitalis and diuretics in patients actually
14 not taking ACE inhibitors. This is based, indeed, on data
15 that we feel are convincing, that are mortality data and
16 ejection fraction data.

17 DR. BORER: Okay. So, you are not specifically
18 suggesting that the drug is indicated for reduction of
19 mortality, but rather that it is indicated in general for
20 treatment of patients with heart failure. Is that right?

21 DR. ORLANDI: We feel that we have demonstrated
22 actually an effect on mortality as well.

23 DR. BORER: I think that Jay is absolutely
24 right, of course. You can't be penalized for not doing

1 what you didn't know to do at the time you did it because
2 the data were not available. I come to these data with a
3 sort of a general bias in favor of the combination being
4 good.

5 However, we are being asked to approve the
6 combination for something here. Now I understand that it
7 is for the general treatment of patients with heart
8 failure, particularly because of mortality reduction. And
9 that may be a good thing to do.

10 But if we are going to do that then obviously
11 everybody has to feel comfortable with the consistency and
12 reproducibility of the effects, and therefore there are a
13 number of statistical considerations that I would like
14 some, again, clarification about here.

15 I don't think that the p values are ironclad
16 rules that one must follow because they say this or that,
17 and I know the FDA regulations aren't written that way
18 either. They are guidelines.

19 On the other hand, we have information really
20 from two trials. One of them was placebo-controlled. As I
21 look at the data, the general Gestalt is that ejection
22 fraction clearly is improved when you give the combination.
23 That is a good thing. Exercise tolerance, well, you know,
24 it doesn't really quite make it statistically but it goes

1 in the right way. That is convincing. And then we have
2 mortality, which is of course a very compelling argument if
3 it is a reasonable one.

4 But that is where this desire I would have to
5 be able to be convinced of the consistency and
6 reproducibility of the results begins to founder a little
7 bit because of statistical considerations that I am not
8 sophisticated enough to really understand.

9 The way I see it, we have a hypothesis that
10 allowed only a one-directional response, maybe reasonable,
11 so we used a one-tailed t-test.

12 We say that there is no penalty for looking at
13 the data many times if you passed a predetermined boundary
14 that was determined by the Data and Safety Monitoring
15 Committee at an early look. That may be right, but I have
16 never heard that before, but maybe it is right.

17 We have multiple pre-specified endpoints and we
18 have no penalty for looking at those, even though they
19 presumably could have gone either way. And that is okay
20 because mortality is so important.

21 But we only have one placebo-controlled trial
22 and then we use a second trial where the placebo is present
23 but it's a historical control.

24 So, all of that is not the way we are

1 accustomed to seeing data, and I would like to have
2 clarified for me whether it is really legitimate to say we
3 don't have to pay a penalty after a pre-specified stopping
4 rule is passed but we decide to go on anyway because we
5 wanted to see if the result was consistent over time.

6 If it is really legitimate not to pay a penalty
7 when we talk about consistency, if there are multiple pre-
8 specified endpoints but there is one that really looks real
9 good. What's the answer to that? Is there a statistician?
10 Lloyd, perhaps?

11 DR. MASSIE: We've heard the answer from the
12 sponsor. I would like to have the answer from our two
13 committee statisticians.

14 DR. COHN: Could I just add one point here
15 because I didn't bring this up before. I am reading now
16 from the V-HeFT I protocol under Sample Size and Duration.
17 "The primary objective of the study is to determine if the
18 survival time is increased on vasodilator therapy as
19 compared to the survival time in the placebo group." That
20 was the primary endpoint. So, don't allow all these other
21 endpoints to dilute that out. It is the primary endpoint.

22 DR. BORER: That is a good point and I accept
23 that.

24 DR. COHN: I would like the response from the

1 agency, but just to remind you, the reason for imposing a
2 penalty for multiple looks is that you always have the
3 opportunity to stop the trial if you surpass the guidelines
4 for the endpoints and the multiple looks.

5 If you surpass the endpoint and don't stop the
6 trial, you really have eliminated the need for any more
7 penalty because you haven't responded to it in the first
8 place. So, the multiple looks have not really contributed
9 to your final decision. That is a nuance, and I would love
10 to hear responses from the statisticians on that, but just
11 intuitively it seems to me that makes sense.

12 DR. MASSIE: Lem?

13 DR. MOYE: I have somewhat a different view.

14 (Laughter.)

15 DR. MOYE: The purpose of corrections for
16 multiple looks is to ensure that you have preserved the
17 type 1 error at an acceptable bound. The type 1 error, I
18 think, is really a cause for lots of concern and lots of
19 confusion.

20 From my way of looking at it, the type 1 error
21 is a matter of population protection. The experimenters
22 have an obligation to protect the population from which
23 they derive their patients and the derived sample. They
24 protect the derived sample, of course, by taking care of

1 the patients as best they can. They protect the population
2 by ensuring that they don't inflict unnecessary false
3 positives or false negatives.

4 The way to provide the insurance for false
5 positives is the alpha level. For every decision that is
6 made concerning a hypothesis test, you have the potential
7 for sampling error propagation, and there are two ways to
8 handle that. The far superior way, again in my opinion, is
9 for the investigators to handle it. That is to say, the
10 investigators must say with absolute clarity what they are
11 going to do with the primary endpoint, how they are going
12 to test it, and what they are going to do with secondary
13 endpoints. They must provide, if you will, a decision
14 path, how they are going to work through the collection of
15 endpoints that they have.

16 They are in the best position to do it because
17 they can do it prospectively. They have an excellent fund
18 of knowledge to do it, but I must confess they are not used
19 to doing that, and perhaps the reason is that we have not
20 asked them to do that. Because we haven't, we find
21 ourselves again in the position of trying to make some
22 determination and some post hoc correction of these
23 accumulated decisions.

24 I think if the investigators surrender their

1 mandate, because that's what they have in the beginning,
2 for controlling these alpha errors to us retrospectively,
3 then it is up to us to come up with our own.

4 My personal one is a very conservative one
5 which penalizes investigators for each decision they make,
6 so that in this circumstance that where the type 1 error at
7 the 2-year interim analysis is very small, then you
8 nevertheless accumulate some error because that decision
9 may have been wrong. You accumulate alpha from that and
10 you move on, so that as one progresses through the
11 secondary endpoints, the alpha eventually accumulates. You
12 stop when you reach the bound, whatever that bound happens
13 to have been. Typically it's at the .05 level.

14 So, I am arguing for, number one, for a
15 prospective plan for the spending of alpha, but in its
16 absence -- and most times I am afraid it is absent -- a
17 very conservative post hoc plan for the accumulation of
18 alpha, and that way we can ensure that the probability of
19 making it at least a type 1 error from all of them is
20 acceptably small for the population at large.

21 DR. MASSIE: Ralph?

22 DR. D'AGOSTINO: I agree very much with the
23 spirit of what was just said, but I would like to add a
24 couple of comments to it.

1 I think this idea of saying you cross the
2 boundary and then you no longer pay a penalty, well, as you
3 cross the boundary you find later on that your mortality
4 for the full study isn't significant. Do you still believe
5 it is significant because you crossed the boundary earlier?

6 Do you start running into making decisions
7 later on that you will change your mind or you will do
8 different things, depending on what those later analyses
9 produce, and you have to have some kind of way of guiding
10 yourself in terms of alpha -- I don't like this notion of
11 alpha spending, but what do you believe about it as you
12 start looking at the data in a further fashion?

13 I think that -- and this is a good example --
14 you have marginal significance with the 2-year mortality.
15 I mean, why isn't it .001 so there was no confusion? It is
16 hovering around. You fuss with one analysis and it crosses
17 over the significance. Another analysis and it becomes
18 slightly better for you. There is not a very comforted
19 feeling on that, and these multiple looks at the data
20 really can't be just dismissed as you have protected
21 yourself earlier.

22 So, I think that we really are in a situation
23 that we can't say you crossed the boundary, therefore you
24 forget about the alpha. I don't think that really is the

1 case here.

2 And I do think that this question that you
3 raise -- and I was trying to say somewhat the same. You
4 come into this study with certain notions that you want to
5 look at survival, and you've seen something that looks like
6 a 2-year survival. Will you see it again? I am not sure
7 you will see it again. I am not sure I am convinced with
8 what the data I have seen here.

9 And I realize that survival is the major thing,
10 but you still carry with you six primary outcomes and what
11 are you going to do with those? Are you just going to
12 ignore them? Those are all sort of look-see. I am not
13 going to think about any significance on them? You
14 certainly are, and once you start playing that game, I
15 think you have to say, how am I going to use my alpha, how
16 am I going to be able to sit back and say, I really believe
17 what I have.

18 And I think that we are left in a situation
19 where we see the survival but I would like to see another
20 test of it.

21 DR. MASSIE: Jeff, do you have more?

22 DR. BORER: No.

23 DR. MASSIE: JoAnn, go ahead.

24 DR. LINDENDFELD: Just in this same vein, I

1 wonder when we use a second analysis to assess mortality,
2 when we know that the first analysis has been borderline,
3 does the second type of analysis need to be stricter than
4 ordinary criteria, once we know that the initial analysis
5 was of borderline significance?

6 DR. D'AGOSTINO: Are you asking me that?

7 DR. LINDENFELD: Yes.

8 DR. D'AGOSTINO: I'm not sure I know the
9 question. Are you saying if they put a second study
10 together?

11 DR. LINDENFELD: I'm sorry. In the initial
12 study, once you know the initial method of statistical
13 analysis was of borderline significance, and we go to a
14 second, already knowing that the first was borderline.

15 DR. MASSIE: This is the log-rank versus the
16 Cox?

17 DR. LINDENFELD: Versus the Cox, right.

18 DR. D'AGOSTINO: No. This is the notion, I
19 think, that was raised in the question, are you looking for
20 the test that is going to do the best for you?

21 DR. LINDENFELD: Exactly. Shouldn't the second
22 be perhaps stricter than if it was primary --

23 DR. D'AGOSTINO: I think so and I think that
24 there is real justification for that.

1 Again, I don't see anything wrong with, say,
2 doing an analysis that makes no adjustment for baseline
3 variables, seeing where that goes, and then doing a sharper
4 analysis that includes covariates to get rid of some of the
5 variability. I am not sure it's imbalances that you need
6 to correct, but you want to reduce some of the variability.

7 But as you progress through that, if it is
8 stated in the protocol that the real analysis that you are
9 going to put your final weight on is the Cox regression
10 that does all the covariates, then I think you can wait to
11 see what that produces.

12 But if your protocol says I am going to look at
13 the log-rank and maybe look at the Cox, or it is unclear
14 what you are going to do with the Cox, and then you really
15 move to the Cox with the hope that it is going to give you
16 some significance because the log-rank didn't, I think you
17 are in a situation where you are beginning to doubt how
18 much certainty you can get from the study.

19 DR. MASSIE: I think the committee has been
20 restive and also very cooperative in not interrupting.

21 We were scheduled for a break, but I would like
22 to try to make a pass-through here and continue the
23 discussion, starting down there. Udho?

24 DR. THADANI: I have a couple of comments and a

1 couple of questions.

2 I want to reiterate, the study of V-HeFT I and
3 V-HeFT II was in class 2 and 3 failures, and only in
4 females, so the application of what we say is only to those
5 groups. There is no data on top of ACE inhibitors from
6 either of the trials.

7 Jay mentioned that the study started in 1980
8 and since we did not know the moving target, it should not
9 be penalized. We learn with experience and the committee
10 has to make a decision what we know now, not what was known
11 before. Life is a penalty. As we get older, we are going
12 to die sooner.

13 Now, Jay mentioned that we don't know why
14 nitrates are used without hydralazine, and I think about 30
15 percent of the patients in CHF have coronary artery
16 disease, in some studies 40 percent. The reason nitrates
17 alone are used are really for 20 percent despite --
18 especially in class 2 and 3 failure, the angina. So, we
19 are using nitrates to treat angina, not necessarily heart
20 failure symptoms. It is difficult sometimes, when they are
21 getting exercise-induced dyspnea, to distinguish how is
22 heart failure versus how is angina.

23 So, I don't think I have much problem why we
24 are not using hydralazine all the time in those patients.

1 That is a comment.

2 Jay, you mentioned in your very earlier
3 statement that efficacy perhaps is not related to
4 hemodynamics, and yet to turn around and you say, well,
5 hydralazine probably prevents tolerance and probably is
6 doing that, so it doesn't jibe.

7 Now, one of the questions on tolerance with
8 nitrates is a moving target. We still don't know what
9 exactly produces it. That is why the sulfhydryl
10 hypothesis, the neurohormones know the oxygen radical, and
11 I could say there are receptors. So, I really don't know
12 what to call this.

13 Now, you are alluding to Dr. Elkayam's study
14 that hydralazine prevented tolerance perhaps rebounding.
15 He is in the audience. I am going to ask him again. I
16 have asked him several times before. There is no
17 hydralazine group in that study and the study was only 24
18 hours. So I have no clue whatsoever what it will do if you
19 do it at 1 week or 2 weeks. Perhaps it might delay the
20 tolerance. By 2 weeks there is no efficacy whatsoever.

21 So, I am not willing to buy that as a data
22 showing that -- postulation, yes, but not a convincing
23 proof that that is how the combination is working. So, I
24 want a comment on that before I say something else.

1 Perhaps you or Uri, who is in the audience, want to allude
2 to it.

3 DR. COHN: Let me see if I can try to express
4 the relationship between hemodynamics and long-term benefit
5 because, yes, I did make the point that the hemodynamic
6 effects that may well influence symptoms in the short term
7 are not necessarily indicative of a long-term benefit.

8 Yes, it is true that nitrates on hemodynamics
9 apparently produce tolerance. Partial tolerance, we would
10 say, because we have done some studies on nitrate therapy
11 chronically and are able to demonstrate that, given with a
12 drug-free interval at night, at 10 or 12 hours at night,
13 that nitrate effect persists.

14 It is true that the benefit that Uri and Leung
15 and others have shown with nitrate co-administration is on
16 hemodynamics and is short-term. So, it provides us a
17 potential mechanism, but it certainly provides us no proof
18 that the long-term benefit is enhanced by the combination
19 and would not also occur with the individual drug. I
20 wouldn't suggest to you at all that these data can be
21 directly extrapolated to the long-term effects of nitrates.

22 Now in our view, the long-term effects of
23 nitrates on left ventricular remodeling are non-
24 hemodynamic. We have data in an animal preparation in the

1 canine that when you administer nitrates for 3 months, you
2 prevent the remodeling of the left ventricle without a
3 demonstrable hemodynamic effect. So, my view is that this
4 mechanism of action of nitrates is through nitric oxide
5 effect either on the interstitium and the collagen, or on
6 the myocyte directly to alter the remodeling process. I
7 think there is growing support for the idea that this
8 remodeling is a non-hemodynamic phenomenon.

9 I have no idea whether tolerance develops at
10 all to that effect. We have no data that hydralazine would
11 influence that effect whatsoever. So like in most drugs --
12 and I think this applies to practically every drug that has
13 been approved by the FDA and that we use daily in practice
14 -- we do not know how they work. Much as we would love to
15 know, we are always grasping at straws to try to find out
16 how drugs such as ACE inhibitors work, or why do beta-
17 blockers lower blood pressure. I have no idea, but they
18 do.

19 So, we have to separate mechanism from efficacy
20 to some extent. We are dealing here with potential
21 mechanisms, but clearly not proof of the mechanism of long-
22 term efficacy.

23 DR. THADANI: Also, I think I would like to
24 point out that ISDN regimen uses four times, which angina

1 is really no better than placebo in several studies. So,
2 it is a very different regimen. So, I would like to
3 suggest let's keep tolerance out of the discussion because
4 you are talking about survival. A combination may or may
5 not be relevant.

6 Now, point two I want to make is that in the
7 V-HeFT II, Enalapril was definitely superior to combination
8 therapy with ISDN hydralazine. There is no way about that,
9 so that is a fact. So, my judgment would be that even --
10 which I use sometimes patients who do not tolerate the ACE,
11 I would hate to suggest that we should put a broad labeling
12 that patients should be -- this is an alternative
13 treatment. I think you have got a study in which you did a
14 study and Enalapril came out ACE or better.

15 So, it's only in patients who are not able to
16 tolerate ACE, not that they are not taking ACE because a
17 lot of physicians do not prescribe ACE, or patients who
18 have renal dysfunction, that might be the way to go.

19 So, I think one has to be concerned when you
20 are looking at the labeling issue.

21 The question was raised in the V-HeFT I. You
22 adjusted, depending on the headache, separately ISDN lower
23 dose without leaving the hydralazine. How are you going to
24 do that with a combination? Do you have any ideas, or what

1 do you suggest we should be doing?

2 DR. MASSIE: Just respond to that last question
3 about the adjustment.

4 DR. COHN: The combination has two different
5 dosage forms which provide different relative amounts of
6 ISDN and hydralazine. So, there is some flexibility
7 available by altering the tablet.

8 DR. MASSIE: John, do you have a question?

9 DR. DiMARCO: I am still a little bit
10 uncomfortable about recommending a combination drug when we
11 do not really have data about either of the agents. Am I
12 understanding you correctly, that you think that nitrates,
13 appropriately administered with a drug-free interval, might
14 produce the same effect you saw with the combination?

15 DR. COHN: There is no data whatsoever on
16 mortality or left ventricular remodeling. All I am saying
17 is that one can maintain the hemodynamic effect of nitrates
18 if you administer them chronically in this patient
19 population with heart failure, measuring hemodynamics. But
20 that has nothing to do with the long-term efficacy that we
21 have demonstrated in this trial. So, the answer is, we
22 don't know.

23 DR. DiMARCO: When you were planning the trial,
24 why didn't you then have a nitrate control group? Or a

1 nitrate group?

2 DR. COHN: This trial was done to prove
3 concept. This was vasodilator concept, and we wanted to
4 use the most potent vasodilators we had available at that
5 time to prove concept.

6 You would never in 1997 design a mortality
7 trial with 640 patients and three treatment arms. Come on.
8 I mean, we are dealing with a different era. We were
9 breaking new ground. We didn't know what the mortality was
10 going to be. We hit actually the placebo mortality right
11 on. That was really our predicted mortality, so we were
12 remarkably fortunate in guessing right.

13 But obviously the study is not powered the way
14 one would power it today, and Dr. D'Agostino is indeed
15 right. Don't we wish we had a larger database from which
16 we could then show a p value that no one would argue with?
17 Wouldn't we wish we had two trials that demonstrated
18 efficacy against a placebo arm?

19 The latter is not possible because we can no
20 longer do a placebo arm. The former we have to live with
21 what we have, and I urge you to remember that p values
22 don't tell you much about the magnitude of effect, but they
23 tell you something about the confidence you would have in
24 that effect.

1 The magnitude of this effect is quite large.
2 The confidence is a little lower because it is a small
3 study, and we have to temper our judgment based upon what
4 we have, and not what we wish we had.

5 DR. MASSIE: Before we cross to the left, Bob?

6 DR. TEMPLE: It is tricky to watch all the
7 dancing p values, but it seems to me one can summarize it
8 by saying the results are analysis-dependent, and that if
9 you make any kind of correction as suggested by Drs. Moye
10 or D'Agostino, it is going to rise above nominal
11 significance. There could be an interminable debate about
12 what that correction should be for the multiple endpoints,
13 the multiple looks, and the fact that it was a three-group
14 study. For starters, you have got to correct for that.

15 So, in that sort of situation one wouldn't
16 ordinarily say that the study is unusable, but one would
17 then look to the next batch of data one has, and in
18 particular look at V-HeFT II.

19 I am interested in people's views about the
20 novel, to say the least, approach to dealing with a study
21 that actually showed inferiority of the drug in question to
22 another therapy, which is not easy to do if you're an
23 active drug, and relies on an imputed placebo group to
24 conclude that even though it was inferior, it probably

1 still had some effect and would have had some effect in a
2 study of V-HeFT II size.

3 Now, that is a very novel argument, as I am
4 sure Dr. Cohn knows, and given the unequivocally borderline
5 at best values in the first study, what does one make of a
6 confirmatory study that loses to Enalapril and has to beat
7 a putative placebo that wasn't there? How plausible is all
8 that? Because nobody is going to make V-HeFT I
9 overwhelming. There are too many things one can say about
10 it. So, it is crucial to know how to interpret V-HeFT II.

11 DR. COHN: I would like to remind you, Bob,
12 that although we all agree that Enalapril beat H/ISDN in
13 V-HeFT II, it only did it at the 2-year time point, not
14 overall. And it was at the 2-year time point where there
15 is much less argument about whether H/ISDN beat placebo.
16 It is the overall p value that we are worried about.

17 So, you can have it both ways. If H/ISDN beat
18 placebo at 2 years, then so did Enalapril beat H/ISDN. If
19 we look at the overall result, neither p value reaches the
20 nominal level of significance, and we have to really look
21 at these two studies then quite similarly.

22 DR. TEMPLE: Jay, even the value at 2 years is
23 not clear-cut. Some of them are, depending on what you do,
24 above .05, some are below .05, but that is completely

1 uncorrected for things that need correcting. At a minimum
2 there is the Prazosin group. You have got to make some
3 correction for that.

4 And I am not one for major corrections for
5 multiple looks here, perhaps, but there were other
6 endpoints and there were multiple analyses, and whatever
7 you think the right correction is, it is borderline.

8 Then at the 2-year time, which was the sort of
9 agreed upon time, it actually lost to another drug. So,
10 you have to believe there is room for it to be somewhat
11 effective but still not as effective as another drug in a
12 study where the overall reduction in mortality was -- I
13 don't know -- like 20 percent. Sorry. You didn't actually
14 measure it. It was likely to be in the neighborhood of 20
15 or so percent based on other Enalapril data.

16 That is a lot to believe. I just wonder what
17 people think about that.

18 DR. MASSIE: Let's move along to the left and
19 see if any of the comments --

20 DR. LINDENFELD: A quick question. In terms of
21 remodeling, in V-HeFT I there was echo data. Was there a
22 difference between the hydralazine-isodi group and placebo
23 in terms of end diastolic dimension over time?

24 DR. COHN: No, the data really were in concert.

1 That is, the LVIDD, I think, as we did it -- and we have
2 improved our methodology since V-HeFT I, but the trends
3 were the same. Clearly, a less precise measurement than
4 the MUGAs that we did sequentially, but the directional
5 changes were the same.

6 DR. MOYE: Just to respond to Bob's question,
7 part of which I think was the notion of comparing to --
8 having an imputed placebo group. I confess to say that my
9 reaction is over negative to that because to me it looks
10 very much like a historical control. There are differences
11 in baseline characteristics between V-HeFT II and V-HeFT I
12 and differences in the choice of medication. I can't say
13 that I have learned anything reliably from that kind of
14 analysis approach.

15 DR. MASSIE: I understand we are going to have
16 a specific presentation relevant to that point by the
17 division after the break.

18 DR. LIPICKY: You have a specific question
19 dealing with that point. It would probably be good to have
20 this discussion at the time that you are answering
21 questions and not when you are trying to clarify the data.

22 DR. MASSIE: Okay. So, Bob, you've prepared us
23 to get ready.

24 DR. WEBER: Jay, I have got a couple of short

1 questions.

2 First of all, you were talking earlier that
3 many clinicians are reluctant to use hydralazine, or simply
4 do not use hydralazine, for treating patients with
5 congestive failure, and that may be partly because, in the
6 minds of many physicians, hydralazine is not always an
7 appropriate drug for patients who have got ischemic heart
8 disease.

9 When you look back at the V-HeFT experiences,
10 what proportion of patients in fact had that failure on the
11 basis of ischemic disease, and was there any information
12 whether the treatment was more effective in those with
13 ischemic disease than those with other etiologies?

14 DR. COHN: No. As I pointed out, about 55
15 percent of the patients in V-HeFT I had ischemic disease,
16 as opposed to 45 percent non-ischemic. The response was
17 quite similar in the two groups. We actually have a slide.
18 I don't think we want to waste our time showing it. But
19 the reduction in mortality in those with CAD and those
20 without CAD was quite comparable.

21 DR. WEBER: Beyond what you showed us -- and I
22 must confess, I had not really been aware in depth of these
23 data before -- that hydralazine may work to prevent the
24 tolerance to the ISDN, do we have enough information to

1 make a comment describing the clinical pharmacology of the
2 product?

3 To me, if we are debating whether or not a
4 combination is appropriate, is there some mechanism that we
5 can reliably put down in writing that would provide
6 encouragement and support for the use of the two drugs as a
7 tandem?

8 DR. COHN: You are talking about blood levels?

9 DR. WEBER: If such were available.

10 DR. COHN: Well, of course there are now a lot
11 of data available because of the bioequivalence issue
12 relating to the BiDil combination and the individual
13 components. If you want to get into that, I could ask some
14 of those that have been directly involved with that to
15 discuss it.

16 DR. LIPICKY: Is that what you want? Blood
17 levels?

18 DR. WEBER: No. I am really looking more for a
19 justification for the mechanism of the two drugs.

20 DR. LIPICKY: How about death? That is what
21 Jay is offering us. If you use them in combination, it
22 saves lives. Isn't that good enough?

23 DR. WEBER: It certainly justifies the
24 treatment. I'm just coming back to --

1 DR. COHN: Well, the pharmacologic mechanism
2 that really led Joe Franciosa and I to use this combination
3 was that when one gave isosorbide dinitrate by itself, the
4 pulmonary capillary wedge pressure fell, and the cardiac
5 output went up only a little bit.

6 When one gave hydralazine alone, the pulmonary
7 capillary wedge pressure barely changed, but the cardiac
8 output went out a lot.

9 When we gave the two together, we got a greater
10 fall in pulmonary/capillary wedge pressure and a greater
11 increase in cardiac output.

12 So, hemodynamically these two drugs are indeed
13 remarkably additive.

14 Now, you have got to put all that aside and
15 say, that was a wonderful idea in 1978 or 1979, but now we
16 understand the mechanism of long-term efficacy in heart
17 failure is not related to that remarkable hemodynamic
18 effect probably and relates to some other action of these
19 two drugs together which favorably affect all these outcome
20 measurements in heart failure. And do we know exactly what
21 they are? I think I know, but I am in a minority and I
22 haven't convinced everybody.

23 DR. WEBER: One last quick question, and it is
24 one that a couple of other people have already alluded to,

1 but I think it is somewhat troubling.

2 The labeling that was initially proposed was
3 that BiDil would be used as an adjunct to diuretic and dig.
4 You then suggested -- your own phraseology was -- that it
5 would be used as an alternative to an ACE inhibitor. Those
6 are slightly different. I don't know if both can be
7 reconciled into one instruction.

8 But bearing in mind the thought that came up
9 and hasn't really been talked about yet, the possibility of
10 a mortality claim, and if that were the case, would the
11 same labeling be in place, or would it just be a general
12 mortality claim that might infer that the drug could be
13 used in patients already receiving an ACE inhibitor?

14 Obviously, we don't have those data, but
15 clearly we have to try and understand how in the real world
16 physicians would interpret these labels. What are we going
17 to say?

18 DR. COHN: Well, as you know, I am a strong
19 advocate of ACE inhibitors to treat heart failure, and I
20 believe any labeling for this drug combination would have
21 to make it clear that ACE inhibitors produce a more
22 favorable effect on mortality and should be employed as the
23 agent of choice in patients with heart failure, and that
24 this would be an alternative for those patients who, for

1 one reason or another, are not using an ACE inhibitor, and
2 that would usually be because of perceived intolerance to
3 the drugs. The instructions for use, then, need to be
4 provided to physicians.

5 But I think the labeling would have to make it
6 abundantly clear that there is a mortality benefit from an
7 ACE inhibitor as compared to this combination.

8 DR. MASSIE: Cynthia? Ray?

9 DR. LIPICKY: I think that it might be useful
10 to say that the exact labeling is something that may get
11 worked out. The thing that is at stake here is whether it
12 should be approved, so that labeling would have to be
13 written.

14 DR. RODEN: (Inaudible.)

15 DR. LIPICKY: Well, I understand that. If you
16 are having trouble deciding whether it has an effect that
17 trials have shown in patients with heart failure, then you
18 are going to have to say it should not be approved. If you
19 are not having trouble in deciding what it does in patients
20 with heart failure, you will be able to tell us how it
21 should be labeled.

22 DR. WEBER: No, I have no trouble deciding that
23 it does something, Ray, I just want to know what it is.

24 (Laughter.)

1 DR. MASSIE: Cynthia?

2 DR. RAEHL: Dr. Cohn, in your experience, would
3 you suggest that the most commonly prescribed of these
4 products would be the two dosages with the 20 milligram
5 ISDN component, based upon what you know was the maximum
6 expected dose in the V-HeFT trials, and what was the actual
7 mean ISDN dose in the range?

8 DR. COHN: Well, I am not sure I could project
9 what dose is going to be used. Physicians tend to use
10 drugs in lower doses than are recommended. It's been our
11 experience with ACE inhibitors that if you tell a physician
12 to use an ACE inhibitor, he or she will use 2.5 milligrams
13 of Enalapril once a day and feel that they have
14 accomplished the therapeutic goal. So, I can't predict
15 which one is going to be used.

16 DR. RAEHL: Well, the reason why I ask -- and
17 perhaps it will come up in the biopharm review, but I would
18 be interested in the prospective comments of the sponsor --
19 is that assuming that many patients will not tolerate 160
20 milligrams of ISDN a day, which I think is a good
21 assumption, then the two middle doses of 37.5 and 20, and
22 75 and 20 could come into play more often.

23 Yet, it appears to me from the biopharm review,
24 we don't have what I would consider the very basic

1 bioequivalency or dissolution data. I must admit, I am
2 quite surprised to see that at this stage of the
3 investigative process.

4 DR. MASSIE: Maybe a focused response on the
5 biopharmacology. Do we have a reasonable 20 milligram
6 component of the nitrates in those pills?

7 DR. ORLANDI: I would probably defer the
8 question to Dr. Forrest who actually performed the studies.

9 DR. MASSIE: You have to come up if you are
10 going to comment.

11 DR. RAEHL: I think to expedite this rather
12 simple yes or no question, whether or not some of that
13 basic bioequivalency data is available for those middle
14 dosages. Or maybe someone from the agency can give a quick
15 answer.

16 DR. LIPICKY: Yes, I should be able to but I
17 can't.

18 DR. MASSIE: I think the question is -- and I
19 think this question is triggered by some concerns in the
20 reviews by the agency, so maybe they can comment -- do we
21 expect to get the same effect from this 20 milligram
22 nitrate component of this pill as they have gotten from
23 isosorbide dinitrate 20 milligrams?

24 DR. LIPICKY: Well, maybe I can address that,

1 and if I say something wrong, holler at me. I am talking
2 to the people who know the data, okay? Because I am
3 recalling it.

4 In the bioequivalence studies, where there was
5 plasma concentration versus time, not in vitro dissolution
6 now, but bioequivalence studies, the to-be-marketed
7 formulation that was studied -- and was it one or two
8 doses?

9 VOICE: Two doses.

10 DR. LIPICKY: Two doses? Low and high? Fine.
11 The lowest dosage form and the highest dosage form, which
12 is usually what we ask people to do, were not bioequivalent
13 to anything. They were not bioequivalent to ISDN as it is
14 available on the market, or hydralazine as it is available
15 on the market, or to either of the formulations that were
16 in either V-HeFT I or V-HeFT II.

17 So, now when I have made such a broad, sweeping
18 statement, what does that mean? It means that the usual
19 generic rule did not apply. It was 21 percent, but it
20 covered a whole range of dosing from 20 to 160 milligrams a
21 day. So, it is still titratable, it still covers plasma
22 concentration ranges that probably one would achieve. But
23 in fact, it is not precisely bioequivalent, so it could
24 never be a generic.

1 So, from my vantage point, I don't think that's
2 a big problem. Since the instructions for use are titrate
3 to maximum tolerated dose -- it isn't, give this dose and
4 then sit back and wait. It is, if that dose doesn't make
5 people say they are sick, give them some more, and if that
6 next dose doesn't make them sick, give them some more, and
7 then they will have a mortality benefit.

8 So, it is titratable. It is dose-proportional,
9 but in fact it is not a generic product.

10 Does that respond to your question or your
11 concern?

12 DR. RAEHL: I think it does, but it also raises
13 the issue once again that even though instructions for many
14 of these are to titrate to maximum tolerable dose, we know
15 we don't do that. That's medical practice.

16 DR. MASSIE: Okay, we are going to try to take
17 a break in about three or four minutes. Let's just get the
18 last two committee members' questions.

19 DR. KONSTAM: I just had a comment and a
20 question. The comment relates to guidelines because with
21 regard to our construct of the guideline with the Agency
22 for Health Care Policy and Research, we grappled a lot with
23 this issue of making recommendations for non-approved
24 products. I think Barry served on that committee, too.

1 I don't think it was the intention of our panel
2 to usurp the role of the agency. I think that we came to
3 recognize that the criteria that we would use to make
4 recommendations were of a different standard than
5 regulatory standard. They were sort of a clinician's
6 surrogate, perhaps, I might call it, if you will. I think
7 we were concerned about safety and we were concerned that
8 some medium level of evidence -- and there were a variety
9 of different levels of evidence that we could use, but
10 would accept therapies that were clearly short of a
11 regulatory standard.

12 Now, having said that, if you are interested in
13 getting people to follow a guideline, I agree with what Jay
14 said, that the current preparations of these agents I think
15 represent really very real practical obstacles to following
16 those recommendations that would be overcome by the type of
17 preparation that's under proposal, that is, if it can be
18 found to meet the regulatory standard. So just to say
19 that.

20 The question I had relates to stopping the
21 trial, or not stopping the trial. I just wonder, why
22 didn't you stop the trial after the fourth look? You're
23 saying at the end that you felt that it was unethical to do
24 another placebo trial because you were convinced of the

1 effect, but why weren't you convinced enough of that after
2 the fourth look?

3 DR. COHN: Well, that is actually a very
4 difficult question and I have grappled with that recently
5 in the light of new concepts that should we have stopped
6 the trial. I think Joe provided a list of the various
7 reasons why the committee in the documents at that time
8 listed why they were not stopping the trial, and obviously
9 it was to learn more about the therapies, learn more about
10 heart failure, learn more about the potential predictors of
11 a favorable response, and to see whether the effect was
12 durable, that is, did it last longer or was this going to
13 be short-term.

14 I think it would have been an appropriate
15 strategy at that point actually, in retrospect, to have
16 stopped randomization for ethical reasons and to continue
17 follow-up, which is an intermediate strategy that has been
18 used in some trials to date.

19 But at that time in 1983, we had no experience
20 in this syndrome, and I was a strong advocate for
21 continuing the trial because it was an important study. I
22 didn't think that the data at that point would be
23 persuasive enough to let everyone in the world be treated
24 with a combination, and therefore we needed to augment our

1 database to learn more about the disease. And we did.

2 But I think you are raising a very interesting
3 ethical dilemma that the committee probably didn't spend as
4 much time agonizing over as they should have.

5 DR. MASSIE: Dan?

6 DR. RODEN: I will take the opportunity to make
7 one comment and then ask a couple of questions. The
8 comment echoes what Bob said, and that is, I am troubled by
9 being asked to approve a compound or a preparation for
10 which the indication is not very clear to me, and which is
11 demonstrably inferior to currently available therapies,
12 although I understand why we're here.

13 So my questions. I have two. One is the
14 question of not mortality but of symptom relief. You
15 showed us some data showing improvement in ejection
16 fraction, improvement in VO₂, and I wonder if you can make
17 some comment as to the sort of clinical significance of
18 those as opposed to the statistical significance of those.
19 The changes seem to me pretty small. So, that was one
20 question.

21 Then the other question has to do with numbers
22 of patients that were excluded from V-HeFT I on the way in.
23 This was touched on earlier with respect to the question of
24 unstable angina, for example, and the reluctance to use

1 hydralazine. I can read the exclusion criteria but it
2 doesn't really say how many patients were actually excluded
3 from the trials on the way in for those kinds of reasons.

4 DR. COHN: Yes. I think there were 3,400
5 patients screened and 640 entered. So, it is about a 5 to
6 1 ratio of screened to entered, if that's what you mean.

7 The reasons for exclusion were down that whole
8 list, of course, and some of them were inability to perform
9 an exercise test or chest pain during an exercise test that
10 excluded them. So, this is a selected population of
11 patients in whom heart failure is causing their symptoms,
12 not some other abnormality of their circulatory system.

13 I think the issue about what the endpoint is is
14 a very important one. From my last or next-to-last slide,
15 I look forward to the day when we will target therapies for
16 specific mechanisms of disease or surrogates for disease,
17 rather than for the disease in general because we throw
18 people into convenient wastebaskets and call this a
19 disease.

20 The labeling for this drug has been proposed to
21 you for heart failure, and we know that heart failure is a
22 heterogeneous syndrome with many different endpoints.

23 DR. MASSIE: Jay, can you make it specific?
24 Ejection fraction, exercise tolerance?

1 DR. COHN: Yes.

2 Now, you asked about peak VO2. There is no way
3 of defining clinically whether a statistical improvement in
4 peak VO2 is really an endpoint that is important or only
5 statistical. As I showed you in V-HeFT II, H/ISDN would
6 have been approved on the basis of exercise performance,
7 statistically significant differences at 3 and 6 months,
8 had this been a 6-month trial.

9 DR. RODEN: You showed us VO2 data. How about
10 exercise time?

11 DR. COHN: Well, VO2 was the primary endpoint
12 defined in the protocol. We have exercise time which
13 follows the same path, but it was VO2 that was really
14 chosen to be the exercise.

15 Now, what we've learned, of course, and what
16 was obviously intuitively apparent to everybody before was
17 that when you do a long-term trial and look at non-
18 mortality endpoints, you get a biased population
19 progressively as the mortality difference enlarges. So,
20 data after 6 months is contaminated by the fact that people
21 are dying and dropping out, and yet you are only studying
22 the exercise in the survivors.

23 And you can put a substitute in, but we didn't
24 do that. We have done that. When you substitute for

1 mortality, and give a low value of exercise to those people
2 who died, which has been done in some trials, you obviously
3 show a benefit of H/ISDN because the people are not dying.
4 And you get a very low value for the placebo group because
5 they have died.

6 So, that to me is not any longer looking at
7 exercise. That is looking at kind of an overall phenomenon
8 which I find contaminated. But that is another endpoint
9 and it could have been used.

10 DR. MASSIE: Just one quick question on my
11 part. It is interesting, if we look at resting VO₂, it
12 sometimes goes up during therapies, particularly
13 sympathetically activating therapy. These differences in
14 peak VO₂ were small enough that they potentially could be
15 explained by a difference in the baseline pre-exercise VO₂.

16 Did you do any statistics or analyses on the
17 VO₂ before exercise?

18 DR. COHN: I can't recall that we did. I think
19 there was no significant change, but I can't recall if we
20 really analyzed that, Barry.

21 DR. MASSIE: I think it is an important issue
22 because although you said directionally the exercise time
23 went in a different direction -- I mean, went in the same
24 direction, the statistics weren't there, and it was, as far

1 as I remember, not even really close to significant at any
2 point in time.

3 DR. COHN: Well, the trouble with an exercise
4 time measure is you have got flat workloads. You can
5 increase by 2 minutes and have the same workload, so that
6 creates --

7 DR. MASSIE: Peak VO2 should be better. I just
8 had that concern because certainly with some of the
9 positive inotropes, I have seen an increase in resting VO2
10 that is equal to the magnitude of the increase in peak VO2
11 that we have seen there.

12 DR. THADANI: One second before you finish that
13 up.

14 Looking at the graphs and the table on VO2 and
15 exercise, VO2 again is a moving target, only showing
16 benefit at 12 months, not other time points, and there is
17 no significance at all on total exercise duration at any
18 time points.

19 DR. MASSIE: Correct.

20 DR. THADANI: So, I think what is important.
21 Before we jump onto whether that is definitely beneficial,
22 I have not seen any benefit.

23 DR. MASSIE: Let's take a 15-minute break, and
24 when we come back, it will be time for people from the

1 agency to make any comments and then we'll go on to the
2 questions.

3 (Recess.)

4 DR. MASSIE: Before we move on to the
5 questions, I do not know if there are any specific comments
6 from the division reviewers that we haven't covered. If
7 there are, this would be a good time to raise any comments
8 and questions.

9 DR. LIPICKY: No, there are not.

10 DR. MASSIE: There are not. Okay. So we
11 thought of everything.

12 Well, I think, then, we should move on to the
13 questions. Maybe as we go through the preamble the rest of
14 the committee will find their place. I am not going to
15 read the whole preamble which basically outlines what we
16 are being asked to consider, the approval of BiDil, and
17 some concerns related to multiplicity, bioequivalence,
18 which I guess we have covered, and tolerance, which we have
19 at least discussed.

20 The first set of questions starts with V-HeFT
21 I, and I will read that in full because I think this is
22 important.

23 Factors that might affect interpretation of the
24 mortality results include the following.

1 There were four interim analyses conducted by
2 O'Brien/Fleming rules.

3 The protocol outlined three possible
4 comparisons in the primary analysis, using the log-rank
5 test. These comparisons included each active treatment arm
6 to each other, the combined vasodilator arms to placebo,
7 each active arm to placebo. Each of these analyses was
8 performed at least once during the course of the study.

9 There were two other analyses: one, a protocol
10 specified Cox regression intended to identify covariates
11 that were important and, two, a retrospective Cox
12 regression analysis for the placebo versus isosorbide
13 dinitrate comparison, using baseline covariates specified
14 by the division. The Cox regression analysis required the
15 somewhat arbitrary imputation of missing baseline values.

16 Mortality was specified to be evaluated as
17 either total mortality over the duration of the study, or
18 as the 2-year mortality, or at the 2-year point.

19 The published description of the study in the
20 NDA submission reported nominal p values. In interpreting
21 the p values for mortality analyses in V-HeFT I, by what
22 factor, if any, should the nominal p value be inflated for?

23 Now, some of these points we have touched on
24 but I think we will revisit them briefly here. My plan is

1 to ask our statistical primary reviewer and consultant to
2 comment first on the statistically related questions, and
3 our clinical reviewer to comment first on the clinical, if
4 I can make that distinction. It is not always so easy.

5 So, I think this first one we will start from
6 the statistical point of view. Lem, multiple endpoints?

7 DR. MOYE: I think I can answer questions 1.1
8 through 1.5 very succinctly.

9 First, I would say that the primary
10 responsibility for setting corrections for endpoints in
11 interim analysis reside with the investigators. I think I
12 mentioned that before. I will just say briefly now. If
13 they don't do it, the responsibility devolves on us.

14 The spending function that I used allocates
15 alpha as the instigators said they would for the primary
16 endpoint. Now, the primary endpoint alpha here is either
17 .09 for a two-tailed test or about .046, I think, for the
18 one-tailed test. That already exceeds the type 1 error for
19 the primary endpoint.

20 Any adjustments that I make to look at
21 additional endpoints, be they primary or secondary
22 endpoints, or times of treatments are going to increase the
23 p values well above an acceptable level.

24 So, I would say that the information that we

1 get from the secondary endpoints here really is not
2 contributory to making this study positive. Now, you do
3 learn a great deal from these analyses and from these
4 evaluations, but it really doesn't add in an important way
5 to making the study positive.

6 DR. MASSIE: Let me just clarify that. In
7 making that statement you are not paying attention to the
8 Cox proportional hazards model of what was stated to be the
9 primary endpoint. Is that correct?

10 DR. MOYE: Right. I was going to hold off on
11 that until we got the question 3.

12 Let me say briefly about that. My read of the
13 protocol is that the analysis plan was to be the log-rank,
14 and to be in a position now where the log-rank says one
15 thing and the Cox regression analysis says something else
16 is pretty intolerable.

17 When I look to get out of that, I look first to
18 see what the investigators said they were going to do. My
19 read of the protocol is that the investigators planned to
20 put most of their weight prospectively on the log-rank.

21 Any other view of that, I think, runs very
22 close to being a post hoc view because we now know what the
23 data show and we now are in a position of having to choose
24 our statistical analysis in view of the data we have before

1 us.

2 The clearest and cleanest answer, I think, is
3 to go with the log-rank.

4 DR. MASSIE: And then let me, just being the
5 devil's advocate, or I don't know what advocate, say, what
6 about the fact the 2-year endpoint log-rank, I think, came
7 much closer than the .09 to achieving statistical
8 significance, at least nominally? Wasn't that the case?
9 What was the log-rank p value?

10 DR. ORLANDI: It was .056.

11 DR. MASSIE: And that is for the two-tailed?

12 DR. COHN: The one-tailed 2-year log-rank was
13 what? We will get that.

14 DR. MASSIE: I guess of the hierarchy of
15 endpoints, mortality was clearly meant to be the first one.
16 My reading, by the way, is that overall mortality was
17 really clear --

18 DR. COHN: The 2-year one-sided p-value log-
19 rank, which was defined in the original proposal, was
20 .0279. There it is: 2-year mortality log-rank .0279.
21 With the Cox model it was .0168.

22 DR. MASSIE: So again, I guess by Lem's
23 criteria that wouldn't affect your answer to these
24 questions either?

1 DR. MOYE: That's correct.

2 DR. LIPICKY: I am not sure that I understood
3 Lem's answer. May I ask you to clarify it so I understand?

4 DR. MOYE: To which part?

5 DR. LIPICKY: Well, to any part.

6 (Laughter.)

7 DR. MOYE: Okay.

8 DR. LIPICKY: Let's take the log-rank of .0279.
9 That is the nominal value. Right?

10 DR. MOYE: I guess I would say arguably,
11 because my view of the protocol was that it was overall
12 mortality and not 2-year.

13 DR. LIPICKY: That's fine.

14 So, that number needs to be adjusted somehow,
15 or does it? That is what 1.1 through 1.5 are asking. That
16 is, if you looked at that number, that looks to me like it
17 is significant, but we know that all of these other things
18 were done in addition to doing that. How should that
19 influence how I look at that number?

20 DR. MOYE: My view, Ray, is that this number is
21 not significant.

22 DR. LIPICKY: Why is that?

23 DR. MOYE: Because the one-sided p value
24 threshold was .025. That's my read. So, this is not

1 significant. They have exceeded their alpha, and so any
2 other decisions I make on any other endpoints are going to
3 further inflate alpha and therefore --

4 DR. LIPICKY: Fine. Then could I pick another
5 analysis where you would not be able to say that?

6 DR. MOYE: You can do anything you like, Ray.

7 (Laughter.)

8 DR. LIPICKY: So, let's forget that the log-
9 rank did meet their prespecified endpoint, and let's pick
10 the Cox model of .0168. So, they didn't prespecify what
11 they had to do. Right?

12 DR. MOYE: Okay. So, now --

13 DR. LIPICKY: So, let's assume that that was
14 the only test that was going to be done.

15 DR. MOYE: Hypothetically they said the Cox
16 model was going to be it and they hit at .0177. Okay?

17 DR. LIPICKY: Yes. That's fine. We'll pick
18 overall mortality, .0177. And that was the prespecified
19 one to do, but all these other analyses were done also.

20 DR. MOYE: Yes.

21 DR. LIPICKY: How should that .0177 be viewed?
22 That's what these questions were meant to get at, okay,
23 because that looks like a pretty significant number to me.

24 DR. MOYE: Right, and the adjustment I would

1 make in the analysis path, going through these endpoints,
2 would be as follows. I would leave the .0177 untouched. I
3 wouldn't snatch defeat from the jaws of victory for the
4 investigation. I would leave the .0177.

5 That does leave me some alpha left to spend on
6 secondary and tertiary --

7 DR. LIPICKY: But I'm not even interested in
8 secondary and tertiary.

9 I guess what this question was oriented towards
10 asking was whether any of these p values for the primary
11 endpoint can be taken at their face value. Am I making
12 sense? Because there were interim analyses, because there
13 was more than one primary endpoint, because there was more
14 than one analysis.

15 DR. MOYE: Okay, I understand.

16 DR. LIPICKY: So, that is what this question
17 was meant to get at, not what your bottom line is.

18 DR. MOYE: Let me handle the interim analyses
19 question first. Decisions are made to continue the trial
20 at prespecified time periods during the trial's duration.
21 That's spending alpha.

22 The way these interim monitoring rules are
23 constructed is that the alpha that you spend is very, very
24 minute. So, in the end, I don't have .025 to spend. Maybe

1 I have .023 to spend. So, from that point of view, the
2 .0177 I think still stands.

3 DR. LIPICKY: It might be .0179 now, though.

4 DR. MOYE: Right.

5 DR. LIPICKY: That's the sort of look that I
6 would like you to give it.

7 DR. MOYE: Now, the issue of having multiple
8 primary endpoints is a little problematic because what is
9 required is a prospective statement by the investigators on
10 how they are going to allocate their .025.

11 Now, if they are planning to allocate .025 to
12 each of them, using kind of a Bonferroni approximation of
13 the overall alpha, the overall alpha exceeds the -- or is
14 at the .05 level, which is unacceptable for a one-sided
15 test.

16 So, the investigators would need to say at what
17 level they are going to accept each of the tests.

18 DR. LIPICKY: But they didn't.

19 DR. MOYE: But they did not.

20 DR. LIPICKY: So, you've got to set it.

21 DR. MOYE: I beg pardon?

22 DR. LIPICKY: So, you have to set it.

23 DR. MOYE: That's right. And so what I would
24 do would be to say, if I have .025 to spend on either of

1 them, that would be for me the probability of making at
2 least one mistake, say a mistake on primary endpoint 1, a
3 mistake on primary endpoint 2, or a mistake on both.

4 I would also say that I want to apportion alpha
5 equally between the two because I do not have any reason to
6 spend it more on one than the other.

7 DR. COHN: They are very interrelated
8 endpoints. Aren't they?

9 DR. MOYE: Well, we're going to get there.
10 Next point is I would also assume that they are
11 independent. Now, that is very conservative and I am doing
12 it for two reasons. Number one, because the investigators
13 let me down and didn't do it up front. And number two,
14 because I don't know exactly what the nature of the
15 dependency is. It is easy to argue about the dependency
16 but I would have to specify exactly what the nature of the
17 dependency is.

18 DR. FISHER: Can I ask a technical question?

19 DR. MOYE: Yes, sir.

20 DR. FISHER: If you perform a randomization
21 test and take the minimum p value, you are absolutely
22 protected by all of our rules and it takes into account the
23 unknown correlational structure. In other words, you let
24 the data tell you, but because you are doing the

1 randomization test, it strikes me when you have highly
2 correlated endpoints, that makes much more sense to most
3 statisticians, I would say, than to assume the worst case,
4 or do a Bonferroni or whatever.

5 DR. MOYE: Well, I guess I am just a little
6 uncomfortable, and maybe most statisticians are not, but I
7 am just a little uncomfortable with the randomization test.
8 I am much more comfortable with -- I am most comfortable,
9 if I can say this, with the investigators saying exactly
10 what they are going to do.

11 Once they have not done that, then the
12 floodgates open and we can all bring our different alpha
13 spending functions to bear.

14 If the question is how I would approach this, I
15 would approach it as I said, and make conservative
16 assumptions because, again, I want to be sure that I am
17 preserving the type 1 error at a minimum bound, considering
18 the issues that have come up today.

19 DR. MASSIE: Let me interrupt. We have a lot
20 of questions and I don't want to get into a technical
21 statistical thing. I think what we're doing now is
22 instructive, Ray, making Lem put his money where his mouth
23 is, so to speak.

24 DR. MOYE: Put my alpha where my mouth is.

1 DR. MASSIE: And we should go through that
2 quickly, and we have a second statistician we are going to
3 bring up the same opinions on. Let's stay away from
4 philosophy and just hit the questions.

5 DR. MOYE: So, Ray, I would work through the
6 very small amount of algebra and I would come up with a
7 number.

8 DR. LIPICKY: Yes, well, can you give a guess
9 as to what that would be?

10 DR. MOYE: Sure.

11 DR. LIPICKY: I guess what I am looking for is
12 some limits here because what you are saying, as I
13 understand it, is that because of whatever was done in the
14 beginning, you are being given the latitude to make the
15 rule anything you want to make it.

16 DR. MOYE: Yes.

17 DR. LIPICKY: So what I am looking for is what
18 that limit would be, and how .0177 fits into that.

19 DR. MOYE: Right. For two primary endpoints,
20 let's say the overall alpha after the interim monitoring
21 was .024. Then I would come up with about .013.

22 DR. LIPICKY: And that is just for two --

23 DR. MOYE: For two primaries.

24 DR. LIPICKY: For two primaries, and there were

1 six.

2 DR. MOYE: If there were six, it would be --

3

4 DR. MASSIE: Come on, Ray. We know that they
5 identified a single primary endpoint.

6 DR. LIPICKY: No.

7 DR. MASSIE: There were not six endpoints I
8 think from the way the protocol was written.

9 DR. COHN: The protocol was written that
10 mortality is the major endpoint of the trial, and it links
11 2-year and overall, which are closely correlated. So, you
12 don't spend all your alpha --

13 DR. LIPICKY: Well, okay, let's be sure we
14 understand exactly what's being said here. There is no
15 question that the trial was sized on the basis of
16 mortality.

17 DR. COHN: And the statement is in the
18 statistical analysis that the primary endpoint is
19 mortality.

20 DR. LIPICKY: Right, but elsewhere in the
21 protocol it says we have these primary outcomes.

22 DR. COHN: It was probably not written
23 properly. They were all listed as primary endpoints but
24 the primary endpoint was really the mortality. The others

1 should have been listed as secondary, and they weren't.

2 DR. LIPICKY: Fine.

3 DR. COHN: I plead guilty.

4 DR. LIPICKY: Okay, so that's for that.

5 And then for the multiple statistical methods,
6 do you need make some other correction because the problem
7 is we have all these analyses to look at and some of them
8 look pretty good.

9 DR. MOYE: Well, the correction I make really
10 is one that frankly ignores the other analyses. I go
11 exclusively by what the investigators said they were going
12 to do. I rely on their diligence and their efforts in
13 putting together an acceptable protocol, and that means --

14 DR. LIPICKY: Right, but I said that it was
15 okay for them to do a Cox analysis.

16 DR. MOYE: Yes. I don't know why.

17 (Laughter.)

18 DR. LIPICKY: And so since I said it was okay,
19 they did it and now I have another p value. What am I
20 going to do with that?

21 DR. MOYE: My advice to you, sir, is to ignore
22 it.

23 DR. MASSIE: Let's just say that they made the
24 point and said, they are both very important and if either

1 one comes up positive, we are going to call it a positive
2 trial. Let's say they have written it that way because
3 some might read it that way.

4 DR. MOYE: Okay. Well, if they had written it
5 that way, then I would have them apportion alpha for each
6 of those tests that they did. Here I think I guess I would
7 be a little more amenable to the point that Jay brought up
8 about there being correlation here. I am not sure I know
9 exactly --

10 DR. LIPICKY: Okay. I think I understand what
11 you are saying and I have it in perspective with respect to
12 these two numbers and that is fine now, as far as I am
13 concerned. If Dr. D'Agostino might comment a little bit.

14 DR. MASSIE: Let's take Lem off the hot seat
15 and have Ralph comment on those five sort of statistical --

16 DR. D'AGOSTINO: When I was dean of the
17 graduate school at BU, the faculty would come in or the
18 chairman would come in and you would expect from the
19 sciences this rigorous evaluation of their faculty for
20 salary increases, and you would expect maybe the people
21 from humanities would be a little bit more loose about it.

22 Well, what used to happen is that the
23 humanities would come in with these scales on how they
24 rated their faculty and the mathematics used to come in and

1 say, this guy is a good guy and so forth.

2 I am a statistician, but I am going to just say
3 this is easy to handle because if I look at the best world
4 that they produce in terms of their hypotheses testing, and
5 you want to do lots of different tests and what have you,
6 none of them are smashing. The levels of significance are
7 not marginal. They are significant by our rules if this
8 was the only thing they are looking at, but they have five
9 or six endpoints to run around with. They have three
10 groups to deal with.

11 Multiply it anyway you please. It really is
12 that once you start saying that there are multiple
13 activities going on here, all of these are levels of
14 significance that they have quickly run you into seven,
15 eight p's of .07 or .9 and so forth, or .09, .10. They
16 quickly get you beyond what we conventionally think.

17 I think that this is a nice study but there is
18 so much going on that nothing comes out that clear that can
19 really stand up to any kind of adjustments that you want to
20 make.

21 I am willing to let them do the Cox regression.
22 I am still not impressed by the final answer they get.

23 DR. MASSIE: Is that good enough for you, or do
24 you want to get specific answers?

1 DR. LIPICKY: That discussion actually answers
2 2 and 3 also. So, you just got through three questions.

3 DR. D'AGOSTINO: Thank you.

4 DR. MASSIE: Maybe I should thank you too, but
5 I think before we jump to 4, if anybody has some burning
6 comments on the committee, let's hear that.

7 DR. TEMPLE: You may well have answered all the
8 questions, but the way this was formed was to see if you
9 could put more specific numbers on at least some components
10 of that, and maybe that's asking a question that's
11 unreasonable and you have to resort to the Gestalt.

12 But, for example, having three groups is fairly
13 specific, three groups with a common placebo. You are
14 going to hear another thing later in this meeting where
15 someone said, well, my critical p value is therefore .035
16 because I have three groups and the common placebo. So, it
17 is not quite Bonferroni because there is a shared placebo,
18 so they are not independent. That is one component of
19 this, surely, that's easy to put a number on.

20 So I guess my thinking was, whatever you say
21 the value here is, you have got it inflate by 50 percent
22 or --

23 DR. D'AGOSTINO: Well, I am trying to say the
24 same thing. Because you have the three groups, there is

1 this sort of multiplication right there. Because you have
2 a number of endpoints, there is a multiplication there.
3 There is no way that I can take this reading that they
4 aren't declaring these as primary endpoints.

5 I know the primary primary is mortality, but
6 the other ones are still called primary and I don't know
7 what that means if it doesn't mean that they are the major
8 variables.

9 DR. TEMPLE: Of course, some of those sort of
10 lean, and I have never understood how, if you have six
11 endpoints and some of them are sort of marginal, you adjust
12 your correction for that. That's for another two-week
13 workshop.

14 DR. MASSIE: Udho.

15 DR. THADANI: Barry, I think one of the things
16 which disturbs me, if we stick to the protocol, that it not
17 show a significant log-rank and then you could show how we
18 can do different statistics to prove the point. I think
19 here we are making a decision on, as has been alluded by
20 the two statisticians, that log-rank was negative and you
21 could bring a lot of tests. I think we have to live with
22 what the data is, and so one has concerns.

23 DR. MASSIE: Yes, I just think, because
24 obviously there are some implications of skipping

1 immediately to question 4 from this, that if you put it in
2 the best light, the protocol did specify two different
3 tests up front. They did give some alpha, specifically for
4 in fact the multiple comparisons, and they did talk about
5 both 2-year and total mortality.

6 My own reaction is, you have to obviously
7 adjust for the groups and if you are willing to let 2-year
8 mortality rise to the level of total mortality -- and it
9 seemed to me there really was a differential emphasis in
10 the protocol -- then you really would have to correct in
11 some way for that and nobody has told us exactly how
12 because I don't think they are totally independent
13 endpoints. You would expect that they would track to some
14 extent.

15 But we have heard our two statisticians tell us
16 that whether they look at it in a quantitative way or in a
17 qualitative way that they are not blown away by the
18 certainty of this result.

19 DR. D'AGOSTINO: Another point to mention here,
20 which I think has been mentioned a couple of times, if
21 there is no guidance in the protocol on how one divides
22 this alpha up, then you can't take the attitude of using
23 the sharpest way of doing it and taking into the
24 correlation and so forth because then you are playing the

1 same game the protocol has played. There is nothing there.

2 If you are going to get to these numbers, you
3 have to take a sort of conservative view. There are three
4 groups, so there's that multiplication. There are six
5 endpoints and there's that multiplication. I don't see how
6 you can get out of that.

7 DR. MASSIE: Okay. Are we ready to move on to
8 question 4?

9 Was there a statistically significant effect
10 found in V-HeFT I for mortality in the entire study, first,
11 and I guess in terms of discussion, 2-year mortality? We
12 might have comments on both of those.

13 Let me ask JoAnn her thoughts, having heard the
14 statisticians' input.

15 DR. LINDENFELD: Well, I think we have heard
16 all of those and it is still very borderline in the best
17 case, that mortality at 2 years or in the entire study
18 period is significant.

19 DR. MASSIE: Any other comments from the
20 committee?

21 DR. THADANI: Are you asking whether you are
22 convinced or not? Is that what you're saying?

23 DR. MASSIE: Yes. We are being asked whether
24 there was a statistically significant effect, having

1 considered what the level of significance might need to be
2 for all of the questions raised in 1, and obviously one
3 would have to, I guess, be persuaded by the Cox more than
4 the log-rank if we were going to say yes.

5 DR. THADANI: We are already implying that we
6 are going to rely more on log-rank, and the answer has to
7 be no, I am not convinced it has shown a benefit.

8 DR. LINDENFELD: And this was discussed in
9 earlier meetings and it was suggested that some
10 confirmatory data would be needed to support this. I guess
11 we will go on and discuss that in a minute. Because of the
12 borderline significance.

13 DR. MASSIE: You mean earlier FDA discussions
14 with the sponsor?

15 DR. LINDENFELD: Right, in earlier FDA
16 discussions.

17 DR. MASSIE: Any comments from the left? It
18 sounds like this is something we need to vote on.

19 DR. LIPICKY: Yes, please.

20 DR. MASSIE: Okay. Let's start down at the
21 left-hand end of the table. We are voting whether there
22 was a statistically significant effect on mortality during
23 the entire study period for V-HeFT I. Dan, you want to
24 lead off?

1 DR. RODEN: No.

2 DR. KONSTAM: Well, I always feel awkward
3 voting on this sort of question because this is the sort of
4 question I ask my statistician, and I haven't heard any of
5 our statistical advisers advise us that the answer to this
6 question is yes, so I don't see how I can vote anything
7 other than no.

8 DR. RAEHL: No.

9 DR. WEBER: Now, this not the 2-year.

10 DR. MASSIE: No. I think they are asked
11 separately.

12 DR. WEBER: In that case, for the moment, no.

13 DR. MOYE: No for the overall.

14 DR. LINDENFELD: No.

15 DR. MASSIE: No.

16 DR. DiMARCO: No.

17 DR. THADANI: No.

18 DR. GRINES: No.

19 DR. BORER: No.

20 DR. D'AGOSTINO: No.

21 DR. MASSIE: Okay. Well, I guess the same
22 question, then. Was there a statistically significant
23 effect found in V-HeFT I for 2-year mortality? I think it
24 is only fair to start at the other end. I don't know

1 whether the other end starts with Ralph or Cindy. We'll
2 let Ralph go first.

3 DR. D'AGOSTINO: Well, if we are consistent
4 with the discussion we had in 1, 2, and 3, we have to say
5 no.

6 DR. BORER: I agree. No.

7 DR. MASSIE: Bob is not allowed to vote.

8 DR. GRINES: No.

9 DR. THADANI: No.

10 DR. DiMARCO: No.

11 DR. MASSIE: Well, I also will have to say no,
12 since I have to rely on the statisticians to some extent.

13 DR. LINDENFELD: No.

14 DR. MOYE: No, for 2-year.

15 DR. WEBER: No.

16 DR. RAEHL: No.

17 DR. KONSTAM: No.

18 DR. RODEN: No.

19 DR MASSIE: Did we get all the way up? Okay.

20 All right, question 5, and Ray, you can at some
21 point tell me if there are other questions we can skip
22 along the way.

23 Was there statistically significant effect
24 found for hospitalizations for cardiovascular causes in

1 V-HeFT I?

2 DR. LINDENFELD: No.

3 DR. MASSIE: Is there any discussion?

4 DR. LINDENFELD: I think it was clearly no.

5 DR. MASSIE: I guess rather than try to find if
6 there is a consensus, we will just vote.

7 Cindy, why don't you start. Oh, I am not sure
8 you were here for all those data actually. You can abstain
9 if you weren't here for that. We are in hospitalizations.

10 DR. GRINES: Actually I did miss that.

11 DR. MASSIE: I think you weren't there.

12 Udho?

13 DR. THADANI: I am not convinced. No.

14 DR. MASSIE: Ralph?

15 DR. DiMARCO: No

16 DR. D'AGOSTINO: No.

17 DR. BORER: No.

18 DR. LINDENFELD: No.

19 DR. MOYE: No.

20 DR. MASSIE: Cynthia?

21 DR. RAEHL: I need a minute.

22 DR. RODEN: We don't have the data.

23 DR. WEBER: Yes, where is this stuff?

24 DR. MASSIE: The data was presented, I believe,

1 for hospitalizations, or at least it was in the package.
2 The hospitalizations were not different.

3 DR. COHN: Yes. No, we didn't claim any --

4 DR. THADANI: Actually it's on FDA packet also,
5 page 18 and 19.

6 DR. LINDENFELD: There's no disagreement about
7 hospitalizations.

8 DR. MASSIE: All right. Is everybody voting?
9 Well, keep going.

10 DR. WEBER: No.

11 DR. RAEHL: No.

12 DR. KONSTAM: No.

13 DR. RODEN: No.

14 DR. MASSIE: One abstention. Right.

15 There were three measures of exercise tolerance
16 in V-HeFT I. For which of these were there statistically
17 significant treatment effects? These are the maximum
18 oxygen consumption, the total duration of symptom-limited
19 exercise, and submaximal exercise duration.

20 Do you want to comment on these?

21 DR. LINDENFELD: I think that total duration
22 was not significant, and the submaximal exercise duration,
23 there wasn't enough data really to evaluate that. Maximum
24 oxygen consumption is certainly of borderline significance.

1 Some points are positive and some are not, so overall I
2 don't think there is a definite overall improvement,
3 although it is very suggestive. Strong trends.

4 DR. MASSIE: Lem, any comment?

5 DR. MOYE: I think if you consider the comments
6 we made about corrections that came out in questions 1
7 through 3, then I look at question 6 about statistically
8 significant. I am thinking statistically significant after
9 making the kinds of adjustments that we have discussed.
10 And after making those adjustments, I don't see that we can
11 say that any of these are significant.

12 DR. MASSIE: I haven't put Bob on the line
13 since he hadn't voted, and you are not allowed to vote. Do
14 you think there is a significant effect on any of the
15 exercise measurements?

16 DR. CODY: (Inaudible.)

17 DR. MASSIE: Jeff?

18 DR. BORER: No.

19 DR. MASSIE: Okay, well, JoAnn has pointed out
20 that the only one probably worth voting on is the maximum
21 oxygen consumption. Maybe we can start down all the way on
22 the left.

23 DR. THADANI: Again, Barry, that is only on one
24 point in time, of all the different points.

1 DR. MASSIE: I think the question is, do we
2 feel that there is a significant effect on maximum oxygen
3 consumption. I guess our thinking should take into
4 consideration the various time points and what was found.

5 Dan, you want to start us off on that?

6 DR. RODEN: Can you state the question?

7 DR. MASSIE: Yes. The question is, was there a
8 significant treatment effect on maximum oxygen consumption
9 at peak exercise during a maximum exercise tolerance test?

10 DR. RODEN: Yes.

11 DR. KONSTAM: I am not sure. Can we hear the
12 statisticians' view of this first?

13 DR. MASSIE: We heard Lem. We didn't put Ralph
14 on line.

15 DR. D'AGOSTINO: If you want to just say let's
16 look at this particular variable -- forget for the moment
17 the multiple testing and so forth -- I had asked the
18 question, okay are you going to do lots of different time
19 points. Do you see a consistency in significance across
20 those time points, and you see a couple here and there and
21 they sort of fade away. So, even in this situation of not
22 getting caught up with the multiple testing, the data is
23 not overwhelming.

24 If you now want to add to the fact that this is

1 in the presence of all these other tests going on, I don't
2 see this is demonstrating significance.

3 DR. MASSIE: Jay showed us the 3 and 6-month
4 data which he said in itself would be enough to -- or was
5 that in V-HeFT II?

6 DR. COHN: The V-HeFT II data.

7 DR. MASSIE: In V-HeFT I it was the 12-month
8 point.

9 DR. THADANI: It's on page 17 of the FDA
10 document. There is only one point which --

11 DR. MASSIE: Yes?

12 DR. RODEN: I was looking at V-HeFT II.

13 DR. MASSIE: Let's start all over.

14 DR. RODEN: Starting all over. That's B20 in
15 the package. For V-HeFT I I think the answer is no.

16 DR. MASSIE: Okay, no.

17 DR. KONSTAM: No.

18 DR. RAEHL: No.

19 DR. WEBER: Yes, I guess I would say no too,
20 but you look long and hard at this and I guess we are going
21 to have the opportunity of revisiting this when we look at
22 V-HeFT II and putting them both together. So, it's no for
23 the moment, is my vote.

24 DR. MOYE: No.

1 DR. LINDENFELD: No.

2 DR. MASSIE: No.

3 DR. DiMARCO: No.

4 DR. THADANI: No.

5 DR. GRINES: No.

6 DR. BORER: No.

7 DR. D'AGOSTINO: No twice.

8 DR. TEMPLE: We didn't actually discuss this,
9 but I have a side question for the committee that sooner or
10 later I think we will have to answer, which is, what would
11 a change in maximum oxygen consumption imply to the
12 committee in the absence of a change in exercise tolerance?
13 Two different measures of the same thing.

14 I don't believe we have ever relied on oxygen
15 consumption as a measure of a symptomatic improvement in
16 heart failure, but it wouldn't be --

17 DR. MASSIE: Well, let me just make a quick
18 answer to that. I know we have been here and we have
19 looked at studies where they have had both, but the oxygen
20 consumption was always the sub-study of overall exercise
21 tolerance. In this particular protocol, oxygen consumption
22 is clearly identified as the primary measure. So, I think
23 following the trend, I would take what the protocol tells
24 us.

1 But if they, for instance, said both equally,
2 how would we weigh one versus the other?

3 DR. TEMPLE: No, I am asking whether you think
4 that is a -- well, you can defer this until afterward, but
5 sooner or later we probably ought to touch on it. Is it a
6 suitable measure of symptomatic improvement? It is an
7 unfamiliar measure of symptomatic improvement, that's for
8 sure, but it still might be reasonable. Sooner or later I
9 think we would like to hear what you think about that, but
10 you don't have to do it now.

11 DR. MASSIE: Okay, well, maybe we won't do it
12 now.

13 Was there a statistically significant effect
14 found for quality of life in V-HeFT I? As I remember, we
15 should probably skip that because the sponsors didn't feel
16 they had seen one either. The measurements were not very
17 precise.

18 Number 8, was there a statistically significant
19 effect found for left ventricular ejection fraction in V-
20 HeFT I? Maybe we'll start with JoAnn.

21 DR. LINDENFELD: Yes, I think there was.

22 DR. MASSIE: Not so much for voting, but I
23 guess discussion purposes.

24 DR. LINDENFELD: Yes, I think at both 8 weeks

1 and a year there was a significant effect.

2 DR. MASSIE: Anybody have any other comments?

3 DR. KONSTAM: I'd like a little bit more
4 clarification of this. Was this one of the predefined
5 secondary endpoints?

6 DR. MASSIE: I think it was one of the
7 predefined -- well, the secondary of the primaries.

8 DR. LINDENFELD: Yes, the primaries.

9 DR. MASSIE: It was a primary endpoint but
10 we've all I think judged it to be below mortality, which
11 was mentioned so often.

12 DR. KONSTAM: Okay, so in that light, I am not
13 sure precisely what this question is asking. Is it asking
14 that question after the correction for the fact that there
15 are five other primary endpoints?

16 DR. LIPICKY: That is correct.

17 DR. MASSIE: That is correct. But we are not
18 voting now. I think this is worthy of some discussion and
19 I see Dan has his hand up too.

20 DR. RODEN: Ray, do you want to put in the
21 labeling, or does somebody want to have this drug indicated
22 to improve ejection fraction?

23 DR. LIPICKY: No. I don't think it is a matter
24 of what the labeling would be or the approval. I

1 understand that. I understand it was a facetious question.
2 But the thing that this was trying to elicit was, what are
3 the positive things you can take away from the trial, and
4 the reasons why one would say that the trial was positive.

5 MS. STANDAERT: Ray, we can't hear you.

6 DR. LIPICKY: Oh, sorry.

7 The reason for the question was to see what the
8 positive things are that one could take away from the
9 trial, and what it would be labeled for would come later
10 once one finally came to the conclusion that the trials
11 found something.

12 DR. MASSIE: So, I guess the question is sort
13 of a totality. Do we think there is an improvement in the
14 ejection fraction and that thought should include all the
15 provisos as to whether we should even be looking at it,
16 because Lem would tell us we should not be looking at it, I
17 guess.

18 DR. LIPICKY: No. What did I say that made you
19 say that?

20 DR. MASSIE: I don't know.

21 I think when somebody said after all the
22 correction and all the rest --

23 DR. LIPICKY: Yes. Well, I think all of that
24 is true. That is, would you look at this trial, and on the

1 basis of the result say that there was an effect on
2 ejection fraction found with some degree of certainty. And
3 that includes everything that we have been talking about
4 all the way along.

5 DR. FISHER: Could I make one technical
6 comment, Barry? The statisticians might like to look on
7 page A130 of appendix 4 of the report because I did a
8 generalized estimated equation analyses with a variety of
9 different models which incorporate all the time points at
10 once.

11 DR. MASSIE: Do you have a page number?

12 DR. FISHER: Yes, A130.

13 The reason for pointing this out is it relates
14 to the relative strength of effect because we have been
15 talking a lot about adjustments and things.

16 DR. MASSIE: I would guess I would interpret
17 this question, or at least I would vote on this question,
18 saying that one could agree that the ejection fraction has
19 been changed, and not agree that that makes it a positive
20 trial. Is that fair?

21 DR. LINDENFELD: Yes.

22 DR. LIPICKY: Sure.

23 DR. KONSAM: There are a couple of different
24 dimensions to this discussion. One of them is what exactly

1 are we being asked, and is it a purely mathematical
2 statistical question. And if that's the case, I might as
3 well pass, and I think a lot of the other people on the
4 panel would pass and just defer to the statisticians to
5 reach a consensus about the mathematics.

6 I guess I would ask Ray, is there a question
7 beyond that? Is there a question that you are asking the
8 clinically oriented reviewers or experts to then look back
9 at the data after the statistical mathematical analysis and
10 ask, okay, do you have reason to believe it now in the
11 context of the mathematics, which is a different sort of
12 question.

13 DR. DiMARCO: I'd like to second Dr. Konstam
14 there. It would be hard for me as a clinician to overrule
15 our two statistical consultants who told me it is hard to
16 find anything statistically positive in this trial. You
17 know, and the question comes up, if you word it as, is it
18 statistically significant, we have already said it is not,
19 essentially.

20 DR. MASSIE: No, I don't think we have. Not
21 for ejection fraction.

22 Bob has got his hand waving.

23 DR. TEMPLE: I didn't hear any reservations
24 from the biostatisticians about ejection fraction. It's

1 significant at four zeros.

2 Maybe you'll tell us you don't like the way we
3 put the questions, but this question was to say, is that
4 real. Not, is it valuable, is it a basis for claims, is it
5 a basis for labeling. None of that stuff. That all comes
6 later. This is, did it happen.

7 DR. KONSTAM: But I think that is important
8 generally with regard to all of these questions because I
9 find myself then, after we ask the purely statistical
10 question, going back and looking at it again and seeing if
11 there's any reason that I would believe, based on
12 pathophysiology, clinical insight, whatever. That maybe it
13 is a marginally mathematically evident piece of information
14 and I believe it because it fits a paradigm that I have.
15 And if that is the question, then we could add insight to
16 that.

17 DR. LIPICKY: Fine. Perhaps all of these
18 questions should be re-worded then and take statistically
19 significant away and say, do you believe it? Is this real?

20 But, you see, the problem is, if you can answer
21 that question outside of the realm of statistical
22 significance, I wonder how you can do that.

23 DR. KONSTAM: I have thought about this, and I
24 think what you do is you bring in the questions about does

1 it fit a pathophysiologic paradigm. Does it fit based on
2 other information that you bring to bear that is not
3 mathematical?

4 DR. LIPICKY: Right, but if the statisticians
5 said that this has a p of .5 and it fit your model, you'd
6 still think it was real?

7 DR. KONSTAM: Not at all. But if the
8 mathematics put it in a marginal zone then I think I would
9 draw upon that set of information --

10 DR. LIPICKY: Fine. So, answer this question
11 in terms of whether you believe it. Is this effect real?

12 DR. MASSIE: And I think that is what we have
13 been trying to do, although I guess there is a varying
14 level of how people answer these questions in terms of that
15 type of thinking.

16 Lem says we shouldn't think about this. I
17 think he means that in a different type of context than can
18 we look at these numbers and decide. I shouldn't be
19 reading into what Lem is saying.

20 But does this make a trial positive is one
21 question. Do we believe that there is a real effect on
22 ejection fraction is a second question.

23 DR. LIPICKY: It should not be looked at from
24 the vantage point of, does this make a positive trial. We

1 have never asked you to count the number of positive
2 trials. So whether you think this is a positive trial or
3 not is irrelevant.

4 DR. COHN: But I'd ask you, Barry, in light of
5 this discussion, to go back to the mortality issue and ask
6 the panel whether they think the mortality reduction is
7 real, even if not statistically significant by nominal p
8 values because that is clearly the question that is being
9 proposed by the agency to find out.

10 The p value question only can depend upon Lem
11 and Ralph, but the implication of the reduction of
12 mortality requires the clinical judgment that Marvin has
13 identified.

14 DR. LIPICKY: I'll second that.

15 DR. MASSIE: Okay.

16 DR. TEMPLE: Barry, I want to object. I'm
17 sorry. We are dancing with words here and it is
18 treacherous.

19 If the committee wants to tell us, yes, I sort
20 of believe it, I can't quite tell you why, the p values are
21 all over the map, that is not very helpful to us because
22 that's information we can't use. You can't approve a drug
23 because someone has an emotional reaction to it.

24 These questions all bear on a seasoned

1 judgment, but it's a judgment based on statistical and
2 other considerations.

3 I just want to make one observation. We have a
4 large number of biostatisticians and we think that we share
5 these judgments about -- we clinicians, I mean --
6 adjustments and things like that with the biostatisticians.
7 They know the math in ways we can't even begin to fathom,
8 but how many endpoints are reasonable and things like that
9 are questions that clinicians -- that we feel we have to
10 deal with, and we've never been told by biostatisticians
11 that we don't dare think about those things.

12 So, too much helplessness in the face of good
13 statisticians is not necessary. These are all things that
14 intelligent people skilled in study design can think about.

15 So, the question here was, given the p value
16 .0001 for the ejection fraction data, is there a question
17 about whether that happened? Later on you get to, suppose
18 it did happen? Who cares? That is a different, perfectly
19 important question.

20 But at this point you don't have to really
21 defer to -- you can reach an answer with the advice of
22 your --

23 DR. MASSIE: I think the reason why this
24 question was sort of re-opened is that it may be that some

1 of the newer members of the committee, which is almost
2 everybody, were not thinking along the same wavelengths. I
3 think that is an important thing to clarify.

4 I think when I would think of these questions,
5 yes, you would take the data from the statisticians, you
6 weigh it against what you've seen in the midst of all this
7 morass of information, and you make a clinical judgment.
8 That in fact is how I voted already, but I am not sure
9 everybody else did.

10 DR. TEMPLE: The formulation I had trouble with
11 was, apart from statistical considerations, do you think
12 this works? The clinicians aren't supposed to be apart
13 from the statistical --

14 DR. KONSTAM: Dr. Temple, can I just respond
15 to --

16 DR. TEMPLE: -- supposed to be in light of
17 statistical.

18 DR. MASSIE: Right. Well, is that what you
19 meant?

20 DR. KONSTAM: Can I respond to that? First of
21 all, I agree with you completely. None of us should be
22 saying things that we can't defend by something. So nobody
23 just sort of looks at it and I can't tell you why.
24 Obviously we need to tell you why.

1 The second thing is, I guess all of us feel,
2 okay what do you want from us. I think that there is
3 confusion. I think Barry said it, about is this a purely
4 mathematical question that we are being asked, or is it a
5 question that is based on the mathematics at first and then
6 interpreted with an eye to pathophysiology and clinical
7 judgment. It sounds like you want the latter.

8 Where this really does come to bear, based on
9 some of the discussions among the statisticians that I have
10 heard, there are circumstances of some very, very
11 compelling findings that seem very, very compelling to us,
12 and some of the statisticians say, just don't look at it.
13 I can't deal with this. It's a post hoc analysis and yet
14 it's an enormous finding.

15 Then I think that is the circumstance where we
16 might want to say, all right, but do you believe it anyway,
17 and why.

18 DR. MASSIE: Ralph.

19 DR. D'AGOSTINO: I think what you just said is
20 very important, and what I think I am saying is that that
21 is not present in this study with regard to mortality.
22 When we were talking about the adjustments, the questions
23 1, 2, and 3, they were focused on mortality. No matter how
24 you look at the statistical procedures that they used and

1 put forth to us, any kind of adjustment takes them over.

2 With this particular one, I think any kind of
3 adjustment still keeps it in the statistically significant.
4 We are moving very quickly through these, but don't carry
5 with you that I said or that Lem said that everything is
6 out now because of the multiple testing. This is very
7 significant from a statistics point of view. Then there is
8 the other question.

9 DR. MOYE: Well, certainly, if you just look at
10 the nominal p value. If you just want to confine your view
11 to the nominal p value, as though that was the only
12 evaluation done in this program, then you have to argue for
13 its statistical significance, but that is not the only
14 evaluation done in the program.

15 The question is, what does the p value mean? I
16 mean, if all you will do is look at these nominal p values
17 and say, yes, they are significant because they are less
18 than .05 or less than .01 or .001, then the overall alpha
19 means nothing with that interpretation.

20 I guess I insist that the overall alpha is very
21 important.

22 DR. D'AGOSTINO: No, I am not disagreeing. I
23 am saying that if you apply all the discussion I had a
24 moment ago where I was being very loose about it, I think

1 that you have a very small p to begin with. As you
2 multiply it for other things, you still have a small p .
3 And I agree with you. I am not saying, I don't think
4 anybody is saying that you should look at this as it stands
5 by itself.

6 What I am saying is, when you make all those
7 adjustments, we make a number of those adjustments, this
8 would probably still withstand the rigor of .05.

9 DR. MASSIE: Yes. Let's call this question.
10 Ralph, this is the ejection fraction question. Is there a
11 significant effect on ejection fraction shown in this
12 trial?

13 DR. D'AGOSTINO: Yes.

14 DR. BORER: Yes, I think there is.

15 I would like to add one thing, just a plea to
16 Jay. Anywhere else in the world you can say whatever you
17 want, but in this one building, just building 10 here at
18 the NIH, please don't call the technique you use to measure
19 it MUGA.

20 (Laughter.)

21 DR. MASSIE: With that comment, Cindy?

22 DR. GRINES: Yes, it's significant.

23 DR. THADANI: Yes.

24 DR. DiMARCO: Yes.

1 DR. MASSIE: Yes.

2 DR. LINDENFELD: Yes.

3 DR. MOYE: No.

4 DR. WEBER: Yes.

5 DR. RAEHL: Yes.

6 DR. KONSTAM: I'm not sure. Let me just
7 clarify my answer.

8 I'm not sure on the basis of what I have heard from
9 the statisticians whether it is statistically significant
10 or not.

11 DR. MOYE: I guess we disagree. We have a
12 different point of view.

13 DR. KONSTAM: Exactly. Therefore, I --

14 DR. MASSIE: By the way, I phrased the question
15 without the word "statistically."

16 DR. KONSTAM: Good. So, I believe the data. I
17 think there is an increase in ejection fraction.

18 DR. RODEN: I think ejection fraction rises.

19 (Laughter.)

20 DR. MASSIE: Ray, I'm sorry to have to ask
21 this. Do you want us to vote on whether we think there is
22 a significant effect on mortality without the "statistical"
23 in there?

24 DR. LIPICKY: I think I would like to hear a

1 yes or no vote that takes away the statistically
2 significant part. Did V-HeFT show an effect on mortality
3 compared to placebo? This is the kind of feeling question,
4 so you don't have to break it up into 2-year and total
5 mortality. Was there an observation that makes you believe
6 there was a mortality effect seen?

7 DR. KONSTAM: Now, Ray, could you give us some
8 kind of idea what level of certainty you would like to see.

9 DR. LIPICKY: Statistically significant.
10 (Laughter.)

11 DR. KONSTAM: 60/40?

12 DR. MASSIE: Are you convinced that there is an
13 effect on mortality? I think that is the question.

14 DR. LIPICKY: You have already made it very
15 clear what you think the statisticians think. So, this
16 question is asking you what you think, so that we have it
17 clearly --

18 DR. KONSTAM: Is it pretty clear to us that
19 there is an effect on survival.

20 DR. LIPICKY: Right. Was a survival effect
21 shown.

22 DR. MOYE: Well, we have to be careful about
23 that.

24 DR. MASSIE: I don't think we should say pretty

1 clear. I think you want to know whether we are convinced
2 that there was a mortality effect.

3 DR. LIPICKY: That the trial found an effect.

4 DR. MOYE: But there is no question that in
5 V-HeFT I more patients died on placebo than died on the
6 hydralazine-isosorbide dinitrate. There is no question
7 about that. That's the data. The issue is, what does that
8 mean for the population at large?

9 DR. LIPICKY: Well, yes and no. Well, let me
10 be sure that I am not doing something totally crazy.

11 The committee very clearly indicated what it
12 thought the study showed in a quantitative way, that is, in
13 a carefully considered statistical fashion.

14 The question that I want the committee to
15 address now with just a yes and no vote, is, even though
16 they think that, what does their gut say? And I don't know
17 that we'll pay any attention to your gut, and probably
18 should not, but because this discussion is going on, I
19 would just like to know what the result of that vote would
20 be.

21 DR. MASSIE: Can I rephrase the question, then?
22 Because I think we have to have some quantitative sense.

23 The question I would ask is, if this study was
24 repeated 100 times, are we --

1 DR. LIPICKY: I think that is a reasonable
2 question. Would you expect to find this many times?

3 DR. COHN: You know, it's more than gut, Ray,
4 because we're using an arbitrary p cutoff of .05 and our
5 statisticians -- or whatever number they are using, because
6 it gives us that greater confidence in the result. But
7 even then we are only dealing with 19 out of 20
8 possibilities. And if it is .07 or .08, does that mean
9 it's the same as .9? No, it doesn't.

10 DR. MASSIE: Well, we can't rediscover total
11 philosophy, I think, but I think this is probably an
12 important sort of way for Ray to get some information from
13 the committee which is, do we think that if we did this
14 trial 100 times, that at least 95 percent of the time we
15 would show a convincing level of reduction in mortality.
16 Is that fair enough, Ray?

17 DR. LIPICKY: It is for me.

18 DR. KONSTAM: Can I just throw one other thing
19 in? I guess one might ask, is it convincing to us enough
20 as a very well informed clinician. Would you use it in
21 clinical practice based on everything you know? And to me
22 when you get up around, let's say -- just to set different
23 standards, when you get up around the 60/40, 70/30 level,
24 as long as you are pretty convinced it's safe, you would

1 probably use it.

2 Now, it sounds to me that the FDA requires a
3 higher level of certainty than that.

4 DR. LIPICKY: Well, you have responded to the
5 question of statistical significance. We are not
6 interested in whether or not you would use it. We are
7 interested in you as a scientist and investigator. Are you
8 convinced that this trial, from that vantage point, if
9 repeated, would find an effect, that again you would
10 believe? That's the question.

11 Certainly in the practice of medicine one uses
12 things that one has absolutely no knowledge about at all.
13 I know that.

14 DR. MASSIE: I think we need to move on. I
15 think we need to give this opinion. Everybody should look
16 forward to question 20, which is whether BiDil should be
17 approved for heart failure. That is certainly going to be
18 something where if there is a different answer to this
19 question from the statistical question, then people will
20 have to deal with that somehow.

21 I am going to start down there with Cindy. Do
22 you want to answer this more clinically oriented question?
23 Are you convinced that this drug has a significant, but not
24 necessarily statistically significant, effect on mortality?

1 DR. GRINES: We are back to the beginning of
2 the questions?

3 DR. MASSIE: Yes.

4 DR. GRINES: With V-HeFT I? Actually that is
5 what we have been discussing here, and I think that there
6 does appear to be a clinically significant difference in
7 mortality. Whether it meets the biostatistical criteria,
8 I'm not capable of answering that.

9 DR. MASSIE: Udho?

10 DR. THADANI: I think as an investigator and a
11 clinician, I am having problems. The trend is in the right
12 direction but I am not convinced that it is significant.
13 So if you would repeat the experiment, it may not bear out
14 again.

15 DR. MASSIE: Ralph?

16 DR. D'AGOSTINO: Do you want a comment or do
17 you want a vote?

18 DR. MASSIE: I want an answer.

19 DR. D'AGOSTINO: I just don't see how we can
20 separate all the previous discussion. I think there is no
21 way of knowing. I think the answer you just got was the
22 correct answer. There is no way of knowing. It remains to
23 be seen.

24 DR. MASSIE: That's a no, I think.

1 Jeff?

2 DR. LIPICKY: Was that a yes or no?

3 DR. MASSIE: That was a no. He doesn't feel --
4 he's not convinced.

5 DR. BORER: I would say no also, and I would
6 like to amplify a little bit. I think that if the study
7 were repeated, it's more likely that you would come up with
8 a similar answer than that you wouldn't come up with a
9 similar answer. But the data that have been presented
10 leave me without a reasonable assurance that you will come
11 up on the second try with the same kind of result.

12 Certainly if I were a clinician faced with a
13 patient with congestive heart failure who couldn't take ACE
14 inhibitors, seeing these data and seeing that they sort of
15 trend in the right direction and there is nothing to
16 suggest that they do something bad to people, and the
17 condition is a horrible one with a terrible outcome, I
18 would probably go with this combination of drugs, even
19 though I don't have the strongest of data to support my
20 doing that because I don't have any other options and it's
21 a bad situation and I'm not doing much harm that I can see.

22 But as a regulatory issue, I have to say no.

23 DR. LIPICKY: What do you mean, Jeff? You have
24 sucrose sitting on the shelf.

1 DR. BORER: But I have no data about sucrose.

2 DR. LIPICKY: Yes, you do. Right there in this
3 trial.

4 DR. BORER: They don't even trend in the right
5 direction.

6 DR. MASSIE: Since this is an opinion, we
7 should get Bob's opinion, even if he can't vote.

8 DR. CODY: We're talking about V-HeFT I and not
9 the drugs themselves overall. We're talking about this
10 study. It gets into temporal issues, when the study was
11 conducted, et cetera.

12 I guess all I could say is, when this study
13 came out, it influenced my treatment practices. So, did I
14 think it was significant? Yes.

15 DR. DiMARCO: I agree with Dr. Borer, except I
16 am going to answer yes instead of no, because I just think
17 the level of certainty I have is much less than I usually
18 see for trials that are submitted for approval.

19 DR. MASSIE: I thought Jeff said it very well,
20 too, but I am going to vote no because I do believe that
21 "convinced" for me is informed by statisticians and also by
22 whether I think 95 times out of 100 the same thing would
23 happen, and I am not convinced that that would be the case.

24 DR. LINDENFELD: I am not convinced it would be

1 95 out of 100, although I do believe it might be 70/30.

2 DR. MASSIE: Wait. Is that a yes or a no?

3 DR. LINDENFELD: It's a no.

4 DR. MOYE: I think all roads lead to the
5 statistics here. Whether you say statistically
6 significant, whether you say you are sampling from the
7 population at large, they all lead to statistics and the
8 answer is still no.

9 DR. WEBER: Well, I have a slightly different
10 point of view. First of all, I agree with what Lem and
11 Ralph have said about the statistics. I think we have to
12 acknowledge that there is a right way to do them, and that
13 at the end of play we didn't quite have a statistically
14 significant result, but it wasn't a huge deviation from
15 that.

16 I look at the survival in V-HeFT I on the
17 combination of hydralazine and isosorbide dinitrate. I
18 look at the data from V-HeFT II. It gives me reassurance
19 that that first line is real.

20 DR. MASSIE: No, you're not looking at V-HeFT
21 II.

22 DR. WEBER: No, but I know from a collateral
23 source that this line is probably realistic. It separates
24 from two other lines on the same graph. As far as I am

1 concerned, whether it is 95 percent or 93 percent, I
2 believe that it is clinically meaningful and I would vote
3 yes.

4 DR. MASSIE: Cynthia.

5 DR. RAEHL: One, I don't believe in the
6 infallibility of statistics and that all things lead to
7 that. Looking at the collection of the data, I would
8 suggest, yes, I believe this does suggest a very strong
9 trend.

10 DR. KONSTAM: To the question about whether I
11 am convinced that this is right and reproducible, the
12 answer is no. I would add, however, that it considerably
13 surpasses my usual threshold of evidence that I require to
14 recommend to clinicians to use, so I would readily use it
15 in clinical practice. But am I convinced it's right? No.

16 DR. RODEN: I think the reason we are having
17 difficulty is because if it's real, it's a small effect.
18 It's not a huge effect, and that is why, given what the
19 statisticians have told us and given my bias about a small
20 effect, I vote no.

21 DR. MASSIE: Okay, I hope that nobody remembers
22 we ever had this discussion when we move on to regulatory
23 things.

24 (Laughter.)

1 DR. MASSIE: But I think it's very important
2 because there is a paranoia that we are marionettes and
3 statisticians tell us what to do, and I think the answer is
4 we need to think for ourselves also but listen.

5 With that comment, I think we are down to --
6 where are we? Nine. Headache and blood pressure are
7 consistent. Do you want us to continue with that?

8 DR. LIPICKY: No, you can skip that.

9 DR. MASSIE: Moving on to V-HeFT II, and again,
10 Ray or Bob, you can tell us if we don't need to keep on
11 going on every question.

12 V-HeFT II had no placebo group. The division
13 and the advisory committee have held a successful active
14 comparator trial requires one to conclude that new
15 treatment would have beaten placebo had there been a
16 placebo group, and that the estimated effect size of the
17 new treatment is not less than half of the effect size for
18 the comparator agent.

19 Now, I know that Bob Fenichel has some
20 comments. I think we don't have a great deal of time, but
21 having spent 12 hours of my life listening to this
22 discussion and now being the only one left on the committee
23 that did, there actually has been a discussion and some
24 standards that the FDA has recommended, at least, to

1 sponsors about what it might take to get a drug approved if
2 there is no placebo group in the trial. I wonder whether
3 maybe in three minutes you could summarize that discussion.

4 DR. LIPICKY: I don't think he needs to do
5 anything yet.

6 DR. MASSIE: Yet. Okay.

7 DR. LIPICKY: Let's see if you understand.

8 DR. MASSIE: Okay. One way in which it could
9 be concluded that hydralazine-isosorbide was superior to
10 placebo would be if the combination were superior to
11 Enalapril in V-HeFT II. Was hydralazine-isosorbide
12 dinitrate superior to Enalapril for any of the mortality or
13 exercise endpoints?

14 Okay, any discussion? How about JoAnn?

15 DR. LINDENFELD: No, I don't believe so.
16 There were no overall definite benefits.

17 DR. MASSIE: Any other comments or discussion
18 from the committee?

19 DR. RODEN: The data are more compelling here
20 than they were in V-HeFT I.

21 DR. MASSIE: You have to talk louder or more
22 directly.

23 DR. RODEN: The data looked more compelling.
24 The graphs looked nicer in V-HeFT II than they do in V-HeFT

1 I. So, I would be interested in the statistical opinion
2 with regard to, for example, the change in VO2 or the
3 change in -- what was the other one -- change in ejection
4 fraction.

5 DR. MASSIE: Change in VO2 or change in
6 ejection fraction. Dan is not sure that he hasn't seen
7 something there, I guess.

8 DR. RODEN: Graph B27, for example, in the book
9 looks more convincing than in V-HeFT I.

10 DR. MASSIE: Okay, any other comments? Dan
11 wanted to hear from --

12 DR. RODEN: From Ralph or Lem.

13 DR. MASSIE: So, there are the two pieces of
14 data we have. Since we know there was not an improvement
15 in mortality compared to Enalapril, these are the two.

16 Any other comments? I think we do need to hear
17 from --

18 DR. RODEN: I think this is an important issue
19 because if in fact an improvement in symptoms has been
20 demonstrated using that kind of measure, then it will
21 affect the way we vote on your last question. So, Lem or
22 Ralph?

23 DR. MASSIE: Lem?

24 DR. MOYE: I guess I am furiously calculating

1 here. This is another study now where you do have a
2 positive endpoint on mortality. We're talking about V-HeFT
3 II. Right?

4 DR. MASSIE:

5 DR. MOYE: But it is a positive endpoint in --

6 DR. KONSTAM: In the other direction.

7 DR. D'AGOSTINO: It is in the wrong direction.
8 The competitor beat out the product. It went in the wrong
9 direction.

10 DR. MOYE: Right, and I guess that is what I'm
11 trying to work through now.

12 I would say that perhaps an argument here is
13 admissible. At least from my alpha spending function, it
14 would be admissible to consider it.

15 DR. MASSIE: Ralph?

16 DR. D'AGOSTINO: Are we going to go item by
17 item? It just went in the wrong direction, so --

18 DR. MASSIE: Well, mortality we are not
19 discussing, but what the question asks if I can still dig
20 it up.

21 DR. D'AGOSTINO: Which one?

22 DR. MASSIE: On exercise and presumably
23 ejection fraction, you also concluded -- well --

24 DR. THADANI: You skipped 10 and 11.

1 DR. MASSIE: No, I thought I was reading 10.
2 Mortality or exercise, right.

3 In other words, the question is, since there is
4 no placebo group, how do we interpret it? And the question
5 says, if the drug, BiDil, beat what we think to be an
6 effective comparator, that would be a positive trial.

7 It did not for mortality. So, we're talking
8 about exercise.

9 DR. THADANI: Barry, before you go further, can
10 you allude one thing? Since there is no placebo, we are
11 already saying that we are not going to compare it with
12 historical placebo. I think we should establish that,
13 because our problems with that --

14 DR. MASSIE: No, we haven't said that at all.

15 DR. THADANI: No, but I am just saying, in
16 order to make a rational decision, since there is no
17 placebo, I think there are two active controls and it
18 happened that ISDN-hydralazine was inferior to Enalapril.
19 So as far as mortality, I think we have to accept that.
20 Right?

21 DR. MASSIE: Right. What they are asking is,
22 even though it was inferior to mortality, was it superior
23 to Enalapril for exercise?

24 DR. CODY: In terms of exercise time or O2?

1 DR. MASSIE: Well, I think that they wisely
2 said exercise endpoints. I assume that that was written
3 with some intention.

4 DR. LIPICKY: That was written intentionally
5 that way, yes. You'll have to decide.

6 DR. D'AGOSTINO: I'm not at all convinced by
7 any of the data I see before me. If it is a blanket
8 answer, I would say no.

9 DR. MASSIE: Bob? Jeff? You're not convinced
10 either?

11 DR. CODY: No, not on the O2s.

12 DR. MASSIE: Since as I understand there was no
13 significant difference on the other exercise endpoints, it
14 really is the O2s we are talking about.

15 Any other comments on this?

16 DR. RODEN: But you didn't see data on the
17 other exercise secondary endpoints. So, there is no
18 difference in exercise time or other endpoints, other
19 secondary endpoints, Jay.

20 DR. COHN: All the exercise endpoints trended
21 in the same direction. The primary exercise endpoint was
22 peak VO2 in this trial, and that is the one that achieved a
23 statistically significant benefit of H/ISDN at 3 and 6
24 months.

1 Now, looking at the whole curves, of course,
2 one as a statistician might raise issue about using those
3 two points and disregarding the rest of the curves, but you
4 must recognize as an agency that up to 6 months is the only
5 data you have ever seen before. So, based upon 3 and 6
6 months, you would have approved this drug on the basis of
7 better exercise, peak VO2 than with the comparator agent,
8 which was Enalapril.

9
10 DR. KONSTAM: Is there a statistical approach
11 to determining whether the two curves differ from each
12 other, and should that be applied?

13 DR. D'AGOSTINO: If you have a question that
14 says what happens in 6 months, that can be a very real
15 question and you could apply a technique that solely
16 focuses on that 6 months. Or you could ask a question
17 about the whole curve. You may not want to ask the
18 question about the whole curve. It may just be in
19 particular time points.

20 I'm not looking at that particular time point
21 and saying that's significant and therefore I really have
22 to focus on it. I'm looking at all of the measurements
23 that I have before me. I see something significant here.
24 It's kind of nice, but I have seen a lot of things that

1 aren't significant, and why would I extract this one and
2 believe in it?

3 So, I am not looking at the full curve. I'm
4 trying to look at these significant results in the context
5 of all the other procedures that have been played here.

6 I don't think there is any hope, if you compare
7 those two curves. You may have something if you focused on
8 that beginning part of it.

9 DR. MOYE: I would like to second what Ralph
10 said and add just one other thing.

11 This is difficult for me to interpret
12 independent of mortality data because you are losing
13 patients as you go along the follow-up time. Maybe the
14 patients that you were losing who were dying were ones who,
15 if they had survived, would have had lower EF's. So, I
16 just have a difficult time trying to interpret this.

17 DR. MASSIE: Yes, I think that's an important
18 point. I don't know if Jay has done this.

19 In the first study it was pretty clear that
20 more people, if anything, were dying on hydralazine and
21 isosorbide dinitrate, and therefore the placebo group might
22 be at an advantage, if you look at exercise time. In this,
23 more patients died with hydralazine-isosorbide dinitrate.

24 Was a carry-forward analysis done? In other

1 words, in the people who died, did we look at their last
2 exercise measurement and carry that forward through any of
3 these endpoints?

4 DR. COHN: Well, we don't like doing that
5 because it really implies that patients would have stayed
6 the same had they been alive, and the other alternative is
7 to substitute obviously a low value for those who died. I
8 don't like doing that either because I think that obviously
9 dilutes the data in a favorable direction. But I can't
10 believe it.

11 I think what we've learned since these trials
12 have been done is that you would not choose to do prolonged
13 exercise testing over a long period of time because of
14 differential mortality, and that is why I focus on the 3
15 and 6-month data because there was not differential
16 mortality during those early time points when you can
17 really evaluate the effect of the therapy on a non-
18 mortality endpoint.

19 After 6 months you begin to see a difference
20 that makes it very difficult to interpret, and I am not
21 sure how you do it.

22 DR. THADANI: Barry, can I comment? On the
23 documents you were given from the FDA, if you look on page
24 40, the middle paragraph, it says, "For exercise tolerance

1 and other endpoints related to cardiac function,
2 hydralazine-ISDN had very little advantage over Enalapril
3 for maximum oxygen consumption. Multivariate analysis
4 showed no significant difference between the treatments."

5 So, I think I will go along with that because
6 that's in your documents. All of you have that.

7 DR. MASSIE: What page is that?

8 DR. THADANI: Page 40. Under V-HeFT II, third
9 paragraph.

10 DR. D'AGOSTINO: I told you that without
11 looking at the text.

12 DR. LIPICKY: We can show you that analysis on
13 a transparency, if you'd like. I don't, unfortunately,
14 know --

15 DR. BORER: To be fair, that analysis is over
16 the entire curve, which was the issue that is somewhat at
17 issue.

18 DR. LIPICKY: Does anyone know the page number
19 in the reviews where those tables appear?

20 DR. BORER: Yes, the raw data, 32 and 33.

21 DR. THADANI: And also the p values varied.

22 DR. TEMPLE: Barry?

23 DR. MASSIE: Yes, Bob?

24 DR. TEMPLE: There's another problem with

1 picking the 3 and 6-month time points. If one had observed
2 a benefit accrued only belatedly, one could think of a
3 plausible reason for why that should occur because there is
4 more time to prevent remodeling. You can always think of a
5 good reason for anything. So, unless the 3 to 6 were
6 specifically identified as the time points of interest, you
7 have to worry that you are once again following your nose.
8 Always a problem.

9 DR. CODY: Can I just amplify on my comments?
10 It has something to do with what you raised earlier.

11 This slide shows the peak VO₂'s, and it assumes
12 there was no difference statistically, even biologically,
13 in the peak O₂'s at baseline.

14 The previous graph, which is B26, shows the
15 mean change for the two groups. There the outcome is a
16 little bit different, certainly at least at 6 months. I
17 guess you'd have to wonder what would happen if a placebo
18 group was in there. Would it be negative at 3 and 6
19 months, or would it fall between the groups?

20 So, given that we don't use peak VO₂ all that
21 much as an endpoint independent of exercise time, and with
22 the understanding that 3 and 6 months is as long as perhaps
23 a lot of other trials, so one has to be careful about
24 putting too much weight on the absence of significance over

1 time down the line, it still comes across to me as sort of
2 a weak observation given that exercise time didn't change.

3 DR. MOYE: I guess I would just say, putting
4 together what Ralph has said about the concerns about the
5 multiple time points, and also this differential censoring
6 effect, where patients on the hydralazine-ISDN are more
7 likely to die, and you don't know what their EF's would
8 have been, I am inclined to vote that there is no
9 significant effect here for the change over time.

10 DR. MASSIE: I think there are a lot of
11 questions, and the one that Bob brought up earlier is, if
12 we were to agree that there is an increase in peak VO₂,
13 does that mean that patients feel better, because I guess
14 that is why exercise came into play, as a quantitative
15 measurement of symptoms.

16 There are the multiple points in time.

17 I think it is not a clear-cut issue but I guess
18 we need to vote on this. In the absence of further
19 comment, I think the way we should phrase the vote is, was
20 hydralazine-isosorbide dinitrate superior to Enalapril for
21 any exercise endpoint, or for exercise endpoints?

22 JoAnn, do you want to vote first?

23 DR. LINDENFELD: If we're going to divide them
24 up, I think it was significant for peak VO₂ at 6 months.

1 The FDA analysis doesn't give it quite statistical
2 significance at 6 months. I think it was .1. But the
3 exercise time, and then I think the time and anaerobic
4 threshold were not significant at all.

5 DR. MASSIE: So that is a yes, that -- I think
6 the way, if I can hazard to guess what Ray is asking, is,
7 do we feel exercise capacity was improved in V-HeFT II?

8 DR. LIPICKY: I'm sorry, I was talking to
9 someone else when you were talking.

10 DR. MASSIE: This question, since you didn't
11 say VO₂, are you asking us whether we think exercise
12 capacity was improved in V-HeFT II?

13 DR. RODEN: You are using exercise capacity in
14 a sort of general way. That's the way I interpret your
15 question. My answer is no.

16 DR. MASSIE: We started down there. We'll keep
17 on coming from there.

18 DR. KONSTAM: No.

19 DR. RAEHL: No.

20 DR. WEBER: No. I'd agree with JoAnn. I'm not
21 sure what "in a general way" means but we do have these
22 compelling data with the peak oxygen consumption at 3 and 6
23 months. So, to that extent, I would say yes, I think there
24 is a difference between the two treatments, at least at

1 that point of the study.

2 DR. MOYE: No.

3 DR. LINDENFELD: I think when you combine all
4 three measurements of exercise capacity, the answer is no.

5 DR. MASSIE: I think I'm going to have to vote
6 yes, but there's an important proviso, which is the
7 question I asked Jay. I'd like to see whether the increase
8 from rest to exercise in VO₂ was improved significantly,
9 and if it were, I would feel that is a quantitative measure
10 of exercise capacity, but obviously we are not going to
11 know that today. But I will vote yes, assuming if it were
12 ever to be examined, it were found to be positive in that
13 manner.

14 DR. DiMARCO: I vote yes for the 3 and 6-month
15 time points, but I really can't make a decision about the
16 rest of the study.

17 DR. THADANI: My answer is no. At 3 months
18 it's significant, but the FDA analysis at 6 months, p is
19 .11. So, the answer is no.

20 DR. GRINES: I vote yes for 3 and 6 months.

21 DR. BORER: I would have to say no. I have
22 concern about the 3 and 6-month points too, and again, they
23 sort of just make it statistically, according to the
24 analyses we were given, but no adjustments were made. The

1 entire discussion we had before is applicable here, and the
2 putative difference is relatively small. So, my overall
3 response is that the answer is no.

4 DR. D'AGOSTINO: No.

5 DR. MASSIE: We've got the vote. Maybe we can
6 gain some momentum here now.

7 If hydralazine-isosorbide dinitrate were not
8 superior to Enalapril, it might still be superior to
9 placebo. 11.1, the sponsor argues that an answer to that
10 question would best be derived by comparing the
11 hydralazine-isosorbide dinitrate group to the placebo group
12 in V-HeFT I. The division argues that the best comparison
13 would be with the results of the SOLVD treatment trial,
14 where the magnitude of the effect of Enalapril was
15 demonstrated, or with a combination of the results of SOLVD
16 treatment and V-HeFT I. What is the appropriate placebo
17 group for this comparison?

18 Any questions or comments?

19 DR. LIPICKY: This is for mortality now.

20 DR. MASSIE: Right.

21 DR. MOYE: I guess I have to say I'm extremely
22 discouraged by this question because I think that the
23 analysis that is suggested here is incorrect. We are
24 talking essentially about historical controls, and they are

1 so fatally flawed with differences in therapy, baseline
2 therapy, and baseline characteristics for the groups that I
3 don't think this question is addressable.

4 DR. D'AGOSTINO: I feel like I am being asked
5 if I should kill my brother or my sister.

6 (Laughter.)

7 DR. D'AGOSTINO: I think both answers would be
8 problematic.

9 (Laughter.)

10 DR. THADANI: I think, Barry, without having a
11 placebo control, we can't guess anything. The trial was
12 done. Enalapril was superior, and we ought to just leave
13 it at that. We can't presume what placebo would have done.
14 It could have gone in any direction, so we can't use
15 historical controls.

16 DR. MASSIE: Well, I guess I need to raise the
17 question that the agency is probably asking us not so much
18 about this specific experience, perhaps, but we are in a
19 day where there will be uncontrolled trials, and the
20 division has sponsored a meeting where that has been
21 discussed and how to imply things. It was in the context
22 of thrombolytic therapy where it wasn't possible.

23 DR. LIPICKY: Barry, that's correct, but you
24 have enough drug to consider. So, if you keep going around

1 the questions, the way in which the answers are coming out
2 are answering the question.

3 DR. MASSIE: All right.

4 What is the appropriate placebo group for this
5 comparison?

6 DR. LIPICKY: And what you have said so far is
7 that there isn't any placebo comparison that would be
8 appropriate.

9 DR. MASSIE: And you are happy with that
10 answer? If that isn't an allowable answer, then we should
11 have a vote.

12 DR. LIPICKY: Well, yes. You can always tell
13 us we don't know what we're asking.

14 DR. MASSIE: Bob?

15 DR. TEMPLE: Ray is right about needing to get
16 on with it, but this is one of the most complicated
17 questions in general we face. What do you do when you
18 can't randomize to placebo anymore, which may be is a
19 conclusion reached too soon sometimes, but was certainly
20 the conclusion reached in this case.

21 In the case of thrombolytics, after some very
22 elaborate discussions, anyone who is here will recall 40
23 consultants, each giving their opinion about things at
24 considerable length.

1 In a setting where everyone agreed that it
2 could be expected that the active control would always beat
3 placebo, that conclusion has not been considered here.

4 But in that setting there were rules and
5 approaches suggested that were, at least in the opinion of
6 the committee then, pretty stringent which included the
7 idea that at least 50 percent of the effect of the active
8 control should be retained not by point estimate, to my
9 best recollection, but as a lower bound confidence
10 interval, a very stringent criterion, which basically means
11 the new drug has to be at least a point estimate better
12 than the old one.

13

14 What is interesting about this case, though, is
15 that no one contemplated -- no one clearly thought about
16 doing that where the new agent actually is inferior to the
17 control agent. And the question of whether you can really
18 ever make a persuasive case in that setting is something
19 that bears further discussion. It's plainly very
20 difficult, but you never like to say never.

21 The setting when this was last considered for
22 thrombolytics was quite different. We had four, five
23 trials where there was a regular 2 percent or 25 percent
24 reduction or whatever, and everybody sort of took that as a

1 given, that had there been a placebo, it would have been 2
2 percent worse than the control. The ability to say that
3 here seems much more complicated, to say the least.

4 Now, what is novel here is that Jay has made
5 the argument that you have got a relevant group that is
6 basically treated the same way. It is in the same
7 environment, and it is rather more plausible than most
8 historical controls. That is not a silly thing to say by
9 any means. The question is whether you believe it.

10 DR. MASSIE: I think what we are going to do
11 because we can't recreate the 40-consultant, 12-hour
12 meeting, is to move on to question 11.2, which is, had a
13 placebo been present, does this committee think it is
14 likely that hydralazine-isosorbide dinitrate would have
15 been greater than that of placebo, the effect of.

16 That seems like a concrete enough thing that we
17 could answer, and I guess I heard some discussion and
18 sentiment about that already. So, maybe we can vote.

19 DR. LIPICKY: To my mind, you have already
20 answered that question, if in fact the committee says there
21 is no placebo group you can compare the results to. Then
22 you have already answered the question and you don't need
23 to.

24 DR. MASSIE: No. That was the comment of some

1 individual members of the committee. Do you want us to
2 vote or --

3 DR. KONSTAM: Can I just ask a question? The
4 way you worded this question is different from the way that
5 you worded other questions. You asked, is it likely.

6 I guess this brings me back to asking you, in
7 our own minds, somehow, what level of evidence are you
8 asking at each of these points. I mean, for me, is it
9 likely? The answer would be yes. Am I convinced? The
10 answer would be overwhelmingly no.

11 DR. LIPICKY: Right, but I think we need to
12 take 15 or 20 minutes to get at that. And there isn't
13 enough time. So, I would suggest that we skip this
14 question in its entirety. It is getting nowhere.

15 DR. MASSIE: Okay, sold.

16 Does the mortality of V-HeFT II confirm the
17 findings of V-HeFT I? Do we need to discuss that since we
18 --

19 DR. THADANI: Are we comparing apples and
20 oranges?

21 DR. MASSIE: -- findings of V-HeFT I that were
22 significant?

23 DR. RODEN: I thought we decided that V-HeFT I
24 probably didn't show a mortality benefit versus placebo.

1 So, I don't think this is an answerable question either.

2 DR. MASSIE: Right. That is what I am asking.
3 Should we answer that question?

4 DR. RODEN: Well, the answer is no.

5 DR. THADANI: Barry, didn't you say that since
6 there is no placebo and we have two, we can't even talk
7 about that? So, we are comparing apples and oranges while
8 we are answering the question. It's a moot point.

9 DR. MASSIE: It would seem that question 12 is
10 moot.

11 DR. LIPICKY: It seems fairly straightforward.
12 If you have said that V-HeFT I has no mortality effect,
13 then in fact there is no effect to confirm.

14 DR. MASSIE: Right.

15 DR. LIPICKY: And that would be a very simple
16 answer. I think everyone agrees on that.

17 Anyone who doesn't agree on that, raise their
18 hand.

19 (No response.)

20 DR. LIPICKY: Okay, you're done.

21 DR. COHN: Is no effect the same as a p value
22 greater than .05?

23 DR. TEMPLE: This is probably a mistake. The
24 committee voted that there was no effect clearly shown in

1 V-HeFT I, but when you asked various members what did they
2 sort of grunt-believe, there was a sort of a mixed belief
3 that there might have been a little something going on.

4 One possibility is that V-HeFT II supports your
5 belief that there's a little something going on because you
6 believe the placebo group that has been developed.

7 Another possibility is that in turning out
8 inferior to a drug whose effect is not that large, it
9 actually weakens whatever thoughts you had about V-HeFT I.

10 So, I guess I wouldn't insist on a vote, but
11 some sense of this may help us figure out how to say or do
12 what we say or do. But if you think that's distracting,
13 feel free.

14 DR. MASSIE: It's getting a little distracting.

15 DR. FENICHEL: Bob Fenichel, FDA. Let me see
16 if I can sharpen this question.

17 I think it's wrong to reject the question on
18 the grounds that, having found no statistically significant
19 effect in V-HeFT I, it is intrinsically a non-confirmable
20 trial.

21 Perhaps it's useful to propose a thought
22 experiment. Suppose V-HeFT I had in fact been replicated,
23 say, 40 times, and the question were now, do these 40
24 replications confirm each other?

1 Now, if you had held that V-HeFT I was a
2 complete waste of time, that it showed nothing, not just in
3 a statistical sense, but it didn't give you any sort of
4 feeling as to where the truth lay, then the answer plainly
5 would be, well, no. Now you have just done nothing 40
6 times.

7 But the answer might be, well, V-HeFT I trended
8 in the right direction and gee, if you saw a trend in the
9 right direction 40 independent times, that would be pretty
10 impressive.

11 So, it is possible for a study which shows
12 nothing by itself to be confirmable or not, and that is
13 what this question was trying to draw your attention to.

14 DR. THADANI: The question said V-HeFT II was
15 designed to compare hydralazine with Enalapril has no
16 relevance to V-HeFT I. All you are saying in this
17 particular study, Enalapril was superior to hydralazine,
18 and there is no way of saying that it replicated the V-HeFT
19 I study. I don't know how you can say that.

20 DR. FENICHEL: I think that the facts make it
21 difficult for me to find confirmation in V-HeFT II of V-
22 HeFT I, but I think that it is an askable question.

23 Suppose it were true that Enalapril is known to
24 be immensely better than placebo every time, essentially

1 reducing mortality to 0 from 100 percent, and suppose it
2 were further true that in V-HeFT II the hydralazine-
3 isosorbide dinitrate combination had been associated with,
4 say, 2 percent mortality instead of 100 percent, and it
5 were large enough to be distinguishable, surely, from
6 Enalapril.

7 Nevertheless, you might say, gee, that's pretty
8 good. That really does confirm the kind of trend in V-HeFT
9 I.

10 What I am asking you to do, I think there is an
11 answerable question. I think this is not a null question.
12 V-HeFT I is confirmable or disconfirmable on the basis of a
13 positive control study.

14 Now, you may believe that it was not in fact
15 confirmed by this particular study, but that is a separate
16 answer. I am asking you not to reject the question.

17 DR. MASSIE: So, you are just asking, could you
18 confirm the results --

19 DR. FENICHEL: No. I'm asserting that it
20 couldn't confirm. I am saying --

21 DR. LIPICKY: Maybe the way to put it is, let's
22 say that hydralazine-ISDN significantly beat Enalapril and
23 you are wondering, did ISDN-hydralazine beat placebo in
24 V-HeFT I. I think you could say V-HeFT II confirms V-HeFT

1 I. It turns out it was the converse.

2 So, the question is addressable, okay. It is
3 really a very simple answer I think, and you were making it
4 complicated so I was going to skip it.

5 DR. MASSIE: Well, I think that you heard that
6 the committee didn't feel you could draw conclusions from
7 V-HeFT II about the effect of hydralazine and isosorbide
8 dinitrate on mortality. And therefore, both because there
9 was no finding to confirm, and because they couldn't draw
10 conclusions, it sounds like we have already answered the
11 question.

12 DR. TEMPLE: Barry?

13 DR. MASSIE: Yes.

14 DR. TEMPLE: Let me try again.

15 To those people who thought that V-HeFT I might
16 have been a good lean, do they feel stronger or less
17 strong, having seen the results of V-HeFT II in which the
18 drug was inferior to another agent?

19 DR. MASSIE: Well, there were four of them,
20 according to the vote, and maybe we can just ask them and
21 move on.

22 DR. TEMPLE: Fine. But I think that is the
23 sort of thing we are getting at. Obviously you can't
24 confirm something you didn't believe fully in the first

1 place.

2 DR. GRINES: I was one who thought that the
3 mortality figures looked pretty good for V-HeFT I, but I
4 would say that if there is a 30 percent reduction in V-HeFT
5 I, I would have expected to see some sort of advantage or
6 at least equivalence in the second study.

7 To my knowledge, ACE inhibitors don't reduce
8 mortality by 50 percent, so I am somewhat surprised that
9 isosorbide and hydralazine lost in V-HeFT II. I would say
10 that I am less enthused about the mortality advantage.

11 DR. MASSIE: Okay. Anybody else?

12 DR. WEBER: Yes. One of the things that was
13 impressive to me in the two separate studies, nevertheless
14 done by the same bunch of investigators and using very
15 comparable patients, was that the survival curves on the
16 two studies were virtually superimposable. In fact, they
17 truly were superimposable.

18 So, what happened when you got hydralazine-ISDN
19 in the second study was that you finish up pretty much the
20 same place as the first study. So, whatever the first
21 study showed, I guess the second study wouldn't weaken my
22 belief in the results of the first study. It wouldn't
23 confirm it, but it wouldn't disconfirm it or nonconfirm it
24 either.

1 So, as one of the people who originally said I
2 thought there was probably something in it, I haven't been
3 persuaded to abandon that point of view.

4 DR. MASSIE: Well, there, Bob, you get two
5 sides of the same thing. Can we move on?

6 Exercise capacity was measured by maximum
7 oxygen consumption at peak exercise and total duration of
8 maximum exercise. Results of both measures of exercise
9 capacity in both the division's and sponsor's view gave
10 similar results.

11 DR. LIPICKY: Barry, excuse me. You are
12 anticipating the answer you gave several questions back.
13 It was going to be repeated. But that's okay. You can
14 skip this. You really have already answered it. You just
15 didn't go through it in the detail we wanted. So, we know
16 your answer to this. You can go on to 14.

17 DR. MASSIE: Which was hospitalizations, but as
18 I remember, there were no data to support a reduction in
19 hospitalizations, I mean, within the same absence of a
20 placebo control group. So, maybe there is not much that we
21 need to further do with that. JoAnn?

22 DR. LINDENFELD: Right. There was no
23 hospitalization difference.

24 DR. MASSIE: And now we get to the ejection

1 fraction. Was there a statistically significant treatment
2 effect on ejection fraction favoring hydralazine-isosorbide
3 dinitrate in V-HeFT II?

4 DR. LINDENFELD: There was at 3 months but not
5 thereafter, so I think overall probably not.

6 DR. MASSIE: Anybody feel otherwise?

7 (No response.)

8 DR. MASSIE: Is that okay, Ray?

9 DR. LIPICKY: Yes.

10 DR. MASSIE: How compelling is the evidence
11 that hydralazine prevents the occurrence of tolerance to
12 isosorbide dinitrate? Do you want us to discuss that?

13 DR. LIPICKY: Yes. Well, all right, no.

14 (Laughter.)

15 DR. LIPICKY: Skip it.

16 DR. MASSIE: I don't think you will get a
17 definitive answer out of this committee.

18 DR. KONSTAM: Can I ask Jay a question about
19 this? You talked about data from your remodeling model
20 with nitrates showing benefit without hydralazine. Isn't
21 that right? How then would you argue that perhaps the
22 remodeling endpoint requires the protection from tolerance?

23 DR. COHN: Well, the data in the animal model
24 were done with isosorbide 5-mononitrate given twice daily.

1 We don't suggest for a moment that ISDN by itself on
2 remodeling would necessarily induce tolerance. For those
3 who think that it may -- and I think Ray has been very
4 concerned about the tolerance issue -- at least we have a
5 mechanism by which this combination might inhibit tolerance
6 and we don't know in humans, of course, whether the
7 tolerance is a major issue or not. I think all those
8 things are true.

9 I think it's important to point out when we get
10 to the ejection fraction data, although that has never
11 served as a provable indication for the treatment of heart
12 failure, that there is remarkable congruence in all trials
13 between the change in ejection fraction and the change in
14 mortality.

15 There is in the animal model that I have
16 alluded to clear evidence that nitrates and ACE inhibitors
17 block remodeling that an alpha blocker equivalent to
18 Prazosin that we used in V-HeFT I does not, despite the
19 fact that it has a hemodynamic effect. So, there is
20 incredible congruence between mortality effects, long-term
21 changes in ejection fraction, and the drugs that one uses.

22 So, although this is not ready yet I think for
23 an indication, I think it should be strongly considered as
24 clear evidence that a drug is altering the natural history

1 of the disease.

2 DR. MASSIE: What about digoxin?

3 DR. COHN: We haven't studied digoxin in our
4 model.

5 DR. MASSIE: In your model, but in the human
6 it's a drug that increases ejection fraction and seems to
7 have a neutral effect on mortality.

8 DR. COHN: Of course, in the dig trial there
9 was no ejection fraction measurement, so we don't know what
10 happened in that trial. The only data we have is up to 6
11 months, which may well be in the right direction. And as
12 you know, in the dig trial there was a reduction of pump
13 failure deaths, but the drug independently has an adverse
14 effect on electrical activity and there was an increase in
15 sudden deaths, probably so. That may well be consistent
16 with the other observations.

17 DR. THADANI: Jay, on that question on ejection
18 fraction, inotropes increase ejection fraction, have a
19 negative effect on mortality. There may be a difference
20 between the mechanism of increasing ejection fraction or
21 vasodilators might be different.

22 DR. COHN: No, there is no data showing long-
23 term improvement in ejection fraction with any inotropic
24 drug other than digoxin, that Barry points out, which we

1 have 6-month data for. But there is no other data.

2 We have data out to 4 years here with ejection
3 fraction, which really is a remodeling phenomenon, not the
4 short-term hemodynamic increase in ejection fraction that
5 may occur when you give dobutamine or amrinone acutely and
6 demonstrate that the heart empties better temporarily, but
7 that is not a remodeling issue.

8 DR. THADANI: Would hydralazine alone do that
9 without nitrates?

10 DR. COHN: We don't know.

11 DR. TEMPLE: Jay, do you know whether if you
12 stop the drug for a couple of weeks, the increased ejection
13 fraction persists?

14 DR. COHN: No, we've never studied that, Bob.
15 That has been studied with the ACE inhibitor. When one
16 stops the drug, the benefit persists so that it isn't all
17 hemodynamic. It's structural. But we've never done that
18 with hydralazine and isosorbide dinitrate.

19 DR. TEMPLE: That seems a crucial question if
20 one wants to believe that there's remodeling and all that
21 stuff, to be sure you separate out the hemodynamic effects.
22 But you think it probably would persist?

23 DR. COHN: Oh, I think a lot of it will because
24 it is a structural change. It's not a hemodynamic change.

1 I think we know very well from a lot of basic studies that
2 that is a change in myocyte length and interstitium which
3 really would persist when one stops the drug, at least for
4 a period of time.

5 DR. CODY: Of course, the other paradox here is
6 that even though the ejection fraction goes up, we can't
7 really attach a mechanism to it. I think people implicitly
8 attach that contractility is improved. The paradox is
9 that, to pick up on Udho and Jay's point, positive
10 inotropes do not uniformly increase ejection fraction,
11 whereas beta-blockers, at least in a number of trials, do.
12 So, if the beta-blocker is increasing the ejection fraction
13 is it by positive inotropic effect?

14 DR. MASSIE: I guess we will hear more about
15 this.

16 Okay, the next set of questions I'm not sure is
17 relevant at this point, that is, getting into the details
18 of the dosing and instructions.

19 DR. LIPICKY: Fine. Why don't you just go on
20 to --

21 DR. MASSIE: We could go back to 17.

22 DR. LIPICKY: Well, go on to the last question.
23 That's fine.

24 DR. MASSIE: So, I think the last question is,

1 should BiDil be approved for use in the treatment of
2 congestive heart failure?

3 Again, I guess any discussion. We'll start
4 with JoAnn.

5 DR. LINDENFELD: I think given all the
6 discussion that we're not certain of the benefit, it would
7 be hard to recommend it. So, I would vote no.

8 DR. KONSTAM: Barry, are we discussing or are
9 we voting yet?

10 DR. MASSIE: Discussing.

11 DR. KONSTAM: I guess the question that I have
12 in my mind is, is there a circumstance where the FDA would
13 consider a lower standard for approvability than is normal,
14 because in my mind the data clearly do not reach the usual
15 level of approvability statistically, or on the basis of a
16 clinical judgment of a certain finding, or a clearly
17 reproducible finding.

18 I guess the arguments in my mind that perhaps
19 the FDA might consider a lower threshold here are some of
20 the arguments that Jay made. This is a study that was done
21 a long time ago that cannot be reproduced. The data trend
22 strongly in the right direction. There is not a
23 significant concern about safety. The finding in favor of
24 survival at least tracks with some other things like the

1 ejection fraction, which often goes along, and the study
2 cannot be reproduced at this point.

3 For all of those reasons, I think if there were
4 a circumstance where the FDA would consider a lower level
5 of approvability than the usual, I think this might be one.

6 DR. THADANI: I think, realizing the study was
7 done in 1980 but we learn with experience so we can't say
8 what we have learned we are going to ignore and go on the
9 evidence or the judgment made in 1980.

10 One of the worries I have, you are going to
11 lower the standard of approvability. Once you start that,
12 there is no end to it and you could talk about any trial we
13 do. You've got six endpoints, four endpoints, one is
14 positive, you are going to approve it. So, I think I've
15 got major problems with the previous speaker on that issue.

16 DR. MASSIE: Well, I don't think -- he was
17 asking.

18 DR. TEMPLE: We're actually actively thinking
19 about how much evidence one needs, but there were a couple
20 of things that are worth saying. There isn't any magic p
21 value. There are conventions but we don't sit here and say
22 if you're .053, you're toast, or something like that. It
23 doesn't work that way.

24 From time to time, although I don't know if

1 everybody would agree, we've actually accepted one-sided
2 tests. The approval of nifedapine for unstable angina was
3 done with a one-sided test because we thought we were
4 confirming something. I just thought I'd mention that. We
5 don't usually do it, but that's really a convention. It's
6 not written in stone. There isn't any law or regulation
7 that says the p value shall be .05 two-sided or .025 one-
8 sided. It's a convention and it represents a strength of
9 evidence. So, that's one thing.

10 Everybody knows that from time to time we have
11 accepted persuasive, unreplicated findings as a basis for
12 approval. That usually involves a clear mortality effect
13 and it usually involves very low p values so that they are
14 persuasive in one way or another on their own.

15 The discussion has been very interesting. I
16 think, from my point of view, we'd have a rather more
17 difficult time if all we had was V-HeFT I because then
18 you'd have a marginal -- then everybody would look and say,
19 well, it's sort of close and it's mortality and you can't
20 do it again and all that.

21 To me it's why I keep pressing this question.
22 The existence of V-HeFT II is, relatively speaking, quite
23 damaging because it isn't easy to lose to another active
24 drug, if you're active. Those studies are not very

1 sensitive to do that.

2 So, when you talk about lowering the standard,
3 the question is, what does that mean and what do people
4 have in mind?

5 There isn't any absolutely rigid standard, as
6 anyone who has followed these committee meetings can easily
7 deduce. But there is some sense that you're supposed to
8 believe it with a reasonably high level of assurance, and
9 we get advisory committees to help us figure out what that
10 level of assurance ought to be.

11 But there isn't a whole lot of credit given
12 because it's old, because the study was smaller than it
13 would have been if they were really thinking about a
14 mortality trial. Those are just the facts of life and it's
15 hard to give credit for that because when it's too small,
16 that means you don't really know the answer. It's not that
17 the answer would have been the same but more significant if
18 you had done a bigger study. You don't know that.

19 So, those are just some thoughts. We are
20 actively trying to write down the sorts of things we think
21 about when we consider evidence.

22 One thing we definitely can do is think about
23 the relevance of pharmacologic activities of short-term
24 studies and things like that. We can do that. The

1 question we will put to advisors is what cases we should do
2 that in.

3 DR. MASSIE: Bob?

4 DR. CODY: Of course, any decisions along these
5 lines today not only affect deliberations for future trials
6 but maybe as soon as this afternoon. So, I think there is
7 a difference here.

8 This is not a new drug or a new drug
9 combination. When I said no for the statistics but yes to
10 how it influenced me clinically, back in the 1980s this
11 V-HeFT I was the final nail in the coffin for Prazosin.
12 So, I wasn't alone in that decision. Everybody else in
13 heart failure stopped using Prazosin. So, people voted
14 with their guts for V-HeFT I a long time ago.

15 V-HeFT II, I would agree, is sort of a negative
16 in the sense that while, yes, the combination was better
17 than placebo, but it looks like Enalapril is better than
18 this combination. However, it looks like because of the
19 exercise, maybe the combination of Enalapril and
20 hydralazine and nitrates would be beneficial. That remains
21 untested. So, we can't really address that at all.

22

23 So, I think what we are looking at is a drug
24 combination that we do have a lot of historical information

1 about. We know, as Jay has pointed out, that there has
2 been no really serious adverse effect with this combination
3 sufficient enough to raise it to everyone's level of
4 consciousness.

5 This has been approved by three guideline
6 groups as an effective alternate therapy. The drug
7 combination suggests we put brackets around a totally
8 loosely uncontrolled range of drug combinations of
9 hydralazine and nitrates that are being used out there.

10 I think that the data that was presented does
11 suggest that the combination of hydralazine with the
12 nitrates attenuates the adverse effects of nitrate
13 tolerance.

14 So, I don't think we're being asked to really
15 necessarily here make with our decision something that's
16 going to "lower the standards" for future deliberations,
17 even as soon as this afternoon. So to address Marv's
18 question, Dr. Konstam's question, I think this might be a
19 case for the reasons that he mentioned and I've mentioned,
20 where one might look at this combination differently and,
21 at the same time, not lowering the standards for how a new
22 drug coming here might be evaluated.

23 DR. MASSIE: Jeff?

24 DR. BORER: I think that all the points that

1 have been made just now by Bob and by Udho are very
2 important, but since the two components are available, and
3 since they are usable if someone believes they are
4 appropriate to be used, I don't think it's necessary to
5 consider changing FDA standards for approvability.

6 The drugs are there, the literature is there.
7 It's not illegal to put them together in a certain dosage
8 form and use them if you believe that's right. The
9 question we're being asked is, are the data supporting that
10 use sufficiently consistent and sufficiently reproducible
11 so that we can recommend that that should be done as a
12 routine procedure by any clinician who wants to do it?

13 I think the answer is, we don't have the degree
14 of assurance that would allow us to do that. Again, if
15 somebody disagrees, the drugs are there, the literature is
16 there. One is free to use these drugs in heart failure.

17 The practical impact of the FDA not approving
18 this combination today is that there won't be an economic
19 incentive for the sponsor to get out and provide
20 educational material for a lot of doctors to know how to
21 use the drugs best. I think that is the impact.

22 DR. CODY: Just along those lines, one of the
23 issues that came up was the need for prescribing
24 information. I think ultimately that's going to be

1 addressed best in labeling.

2 But getting back to our very early discussions
3 -- and Barry raised this -- yes, it might be true that only
4 40 or 50 percent of patients are receiving ACE inhibitors,
5 but that doesn't mean the other 50 percent wouldn't benefit
6 from them. It means that for whatever reason the message
7 isn't out there. So, the use of the term of this as
8 alternate therapy might be a little bit misleading in that
9 regard.

10 At the same time, in the labeling we can't say
11 anything about whether or not this combination is
12 beneficial added to an ACE inhibitor.

13 There are also the minor issues of no data for
14 functional class 4 patients and perhaps even a smaller but
15 I think timely or at least politically correct point, we
16 don't have any information in women.

17 DR. MASSIE: Well, I think we've had some
18 discussion. I think we need to take a final vote on this.
19 Why don't we start on the right there. Cynthia, do you
20 want to lead off the vote on whether this is approvable or
21 should be approved for the treatment of heart failure?

22 DR. GRINES: No.

23 DR. MASSIE: Udho?

24 DR. THADANI: No.

1 DR. MASSIE: Jeff?

2 DR. BORER: No.

3 DR. D'AGOSTINO: No.

4 DR. DiMARCO: No.

5 DR. MASSIE: No.

6 DR. LINDENFELD: No.

7 DR. MOYE: No.

8 DR. WEBER: I'm going to vote yes. I felt that
9 there was enough information provided to give me reasonable
10 confidence that the drug was beneficial or the product was
11 beneficial or would be beneficial in a different
12 formulation.

13 I believe that physicians are being encouraged
14 to use it by reputable agencies that issue guidelines and
15 advice to physicians.

16 I think the availability of the combination
17 would encourage physicians to use hydralazine together with
18 the ISDN rather than just the ISDN alone, which I think may
19 be important to improve the quality of care.

20 And I do not have the same concern that one or
21 two others have expressed about weakening FDA standards. I
22 think FDA standards are absolutely critical when you're
23 considering new molecules or new paradigms of treatment or
24 some kind of definite new step away for what's currently

1 being done or what's currently available. But here we're
2 just finding a way to make more convenient, and I think
3 more efficacious a treatment that's already in use, and I
4 can't see any real down side to approving it.

5 So, that's why I would vote yes.

6 DR. RAEHL: I think the totality of the
7 evidence supports approval of this drug. However, I would
8 say that when we think about labeling that it would be
9 adjunctive to dig and diuretics in the treatment of chronic
10 heart failure in particularly those patients who have
11 sensitivity or demonstrated intolerance to an ACE
12 inhibitor.

13 DR. KONSTAM: I guess I would give the FDA my
14 clear view that this does not meet its usual criteria for
15 acceptability. I think that's very clear to me. I would
16 still vote yes, approval, because I think perhaps this fits
17 into a circumstance that I might lower that standard
18 without, as Mike points out, influencing future decisions.

19 DR. RODEN: No.

20 DR. MASSIE: Well, I think that we've gotten
21 through the agenda, and it's one minute before the
22 scheduled time. So, we should get together by 10 after
23 2:00. That's 40 minutes, and get the discussion started
24 shortly thereafter.

recessed, to reconvene at 2:15 p.m., this same day.)

(2:21 p.m.)

discussing NDA 20-297, Coreg, or carvedilol, for the indication of congestive heart failure. The first part of the presentation will be the sponsor's presentation. If they would like to start, they are free to do so.

DiMarco, Dr. Lipicky, members of the Cardioresenal Advisory Committee, good afternoon. My name is Bob Powell. I'm Vice President for Regulatory Affairs at SmithKline Beecham

1 Pharmaceuticals.

2 We at SmithKline Beecham and Boehringer
3 Mannheim appreciate this opportunity to present the
4 information on the use of carvedilol, Coreg, for the
5 treatment of congestive heart failure.

6 As you know, this meeting represents the second
7 time that the committee has been asked to review carvedilol
8 for the treatment of congestive heart failure. For those
9 of you who were present in May, you will recall that at
10 that time the committee and the FDA agreed that carvedilol
11 SNDA contains one study, study 240, that provides
12 information that would support the approval of carvedilol
13 for heart failure.

14 However, while the results of several other
15 trials were presented at that time, and most of these
16 trials showed favorable effects of carvedilol in a variety
17 of prespecified clinically important measures of efficacy,
18 many of these measures were secondary endpoints in trials
19 that did not achieve statistical significance for their
20 primary endpoint --

21 DR. DiMARCO: Excuse me, Dr. Powell. Can we
22 dim the lights for the front so the slides project better?

23 DR. POWELL: -- in trials that did not achieve
24 statistical significance for their primary endpoint,

1 notably improvement in exercise tolerance.

2 Also, the final report from a major study,
3 study 223, performed in Australia and New Zealand, had not
4 been submitted to the FDA prior to that meeting and thus
5 the committee was unable to fully assess the value of study
6 223 at that time. The committee by a vote of 4 to 2 did
7 not recommend approval of Coreg.

8 Finally, I should add that neither the
9 committee nor FDA raised any significant safety concerns
10 about the use of carvedilol for the treatment of CHF.

11 Since the May meeting, we have submitted and
12 FDA has reviewed three types of new information.

13 First, we submitted the final report of the
14 long-term results of our second major trial, study 223,
15 which we believe confirms the effects seen in study 240.

16 Second, in response to specific requests from
17 FDA, we submitted additional analyses of the effects of
18 carvedilol on morbidity and mortality, as observed in
19 previously reported multi-center trials, studies 240, 221,
20 and 220.

21 And third, we have provided additional
22 information to clarify the effect of carvedilol on CHF
23 symptoms and clinical status. I am pleased to note that we
24 have reached full agreement with the FDA on the data, the

1 analyses, and the nominal p values associated with the
2 carvedilol database that are summarized in your briefing
3 document. What remains, however, is to reach agreement on
4 the proper interpretation of these data and analyses.

5 As part of the meeting, you will be asked
6 several questions concerning the efficacy of Coreg, all of
7 which lead ultimately to the single question, should Coreg
8 be approved for the treatment of congestive heart failure.

9 In examining this question, we wish to
10 emphasize that there is a hierarchy of drug effects that
11 should be considered in deciding if Coreg demonstrates a
12 clinically important effect in the treatment of congestive
13 heart failure. In any hierarchy of benefits, mortality
14 would be the most important. Second would be effects on
15 morbidity, followed by effects on clinical symptoms and
16 status, and finally, effects on hemodynamics.

17 While we are not seeking a survival claim per
18 se for Coreg, it is of note that in the U.S. multi-center
19 trial program treatment with carvedilol was associated with
20 a 65 percent decrease in the risk of death, with the
21 nominal p value of 0.0001. While this observation led to
22 the Data and Safety Monitoring Board's recommendation to
23 terminate the entire program and offer carvedilol to
24 patients taking placebo, we understand that there can be a

1 legitimate debate about the appropriate regulatory course
2 of action for a survival claim based on data from trials
3 not specifically designed to detect a mortality benefit.

4 Nevertheless, this finding does effectively
5 rule out the possibility that carvedilol has an adverse
6 effect on survival.

7 A directionally positive but not statistically
8 significant effect on mortality was also observed in study
9 223, and the overall mortality benefit based on all
10 placebo-controlled trials with carvedilol suggests a
11 relative risk of 0.51, and an overall nominal p value of
12 0.001.

13 In our hierarchy of effects, after a reduction
14 in mortality, evidence of a reduction in the worsening of
15 CHF would clearly be an important benefit. In all of our
16 multi-center trials, we prospectively monitored
17 hospitalization as a measure of worsening CHF. You will
18 find that it is the data on hospitalizations, or more
19 specifically, the combined endpoint of hospitalization or
20 death, that are most convincing that Coreg produces a
21 clinical benefit in these patients.

22 Why the combined endpoint? In fact, the
23 combined endpoint is clearly a better measure of worsening
24 of CHF than hospitalization alone because death is in fact

1 simply the worst possible outcome. If, for example, all
2 patients in one group had been hospitalized and all
3 patients in the other group had died, the conclusion would
4 not be that the deceased group was better off.

5 Thus, we believe that mortality is an
6 appropriate and necessary part of the measure of morbidity.
7 We will provide prospective data from two well-controlled
8 trials and retrospective analyses of data from two
9 additional trials that demonstrate a positive effect on the
10 combined endpoint of morbidity and mortality.

11 The third benefit of Coreg in our benefit
12 hierarchy is the effect of Coreg on the clinical symptoms
13 and status. Data from eight placebo-controlled trials show
14 that Coreg produced consistently favorable effects on each
15 of several measures of symptoms in clinical status within
16 and across studies, including New York Heart Association
17 class, CHF symptoms, and global assessments.

18 In addition, to complete our hierarchical
19 profile, Coreg produced consistently favorable effects on
20 left ventricular ejection fraction measured noninvasively,
21 as well as left ventricular function assessed invasively.
22 Thus, Coreg produces a variety of favorable effects across
23 the entire hierarchy of desirable outcomes for patients
24 with CHF.

1 However, there is considerable variability with
2 respect to the ability to demonstrate any one of these
3 effects in any given clinical study. This raises an
4 important question. How variable are the outcomes of
5 clinical trials of compounds recognized to be useful in
6 CHF?

7 In response to a request by Dr. Temple, Dr.
8 Milton Packer has reviewed the data from the NDAs of all
9 five drugs approved for CHF during the last decade. He
10 found that there was no measure that distinguishes drug
11 from placebo in all trials for any given compound, and that
12 clinical symptoms were significantly improved compared to
13 placebo in only about half of the trials in which they were
14 measured.

15 Further, despite the fact that fewer than 50
16 percent of the trials conducted with these drugs reached
17 their primary endpoint, it was possible to assess their
18 effectiveness on the basis of concordance of findings
19 across trials, including those which failed to reach the
20 protocol-defined primary endpoint.

21 In our presentation today, we will provide
22 evidence from two well-controlled trials that demonstrate a
23 reduction in morbidity and mortality, as well as a
24 concordance of data demonstrating positive effects on

1 clinical symptoms and status, in addition to favorable
2 effects on hemodynamics. We believe that these data meet
3 the usual standard used to assess drugs for the treatment
4 of CHF. In fact, based on this database, Coreg is now
5 available in several countries outside the U.S. for the
6 treatment of CHF.

7 Having said that, we recognize that the
8 carvedilol database does have some limitations, and we
9 would propose that these can be adequately handled in
10 labeling. For example, we believe that one limitation of
11 the current file is the lack of any extensive clinical
12 experience in patients with class IV heart failure.
13 Therefore, we are not at this time recommending that
14 carvedilol be used to treat patients with CHF symptoms at
15 rest, particularly those hospitalized for worsening heart
16 failure or receiving intravenous medications for heart
17 failure.

18 One final comment. In the FDA medical and
19 statistical review, it is noted that carvedilol is, after
20 all, currently approved in the U.S. for hypertension, and
21 it is suggested that since carvedilol could be available
22 for the treatment of hypertension, there is no compelling
23 need to approve carvedilol for CHF at this time, suggesting
24 that physicians would be free to use the drug, off label,

1 for CHF based on peer-reviewed publications that have
2 appeared in the New England Journal of Medicine,
3 Circulation, and most recently, The Lancet, describing the
4 clinical program for carvedilol in CHF.

5 We would take exception to this view,
6 particularly for a drug like carvedilol. Initiation of
7 therapy with carvedilol in CHF requires considerable
8 caution and can be best achieved only if the prescribing
9 physician has substantial knowledge about the associated
10 risks and their management. It is the need for careful
11 titration and a desire to provide the appropriate
12 information to the physician that has resulted in our
13 decision not to launch carvedilol for hypertension, despite
14 its approval for that indication some 17 months ago.

15 We believe that the proper physician education
16 cannot be readily achieved under current FDA regulations
17 without an approved claim for the treatment of CHF, and we
18 are accordingly strongly committed to accomplish this
19 educational task if the drug is approved.

20 With this background, Dr. Neil Shusterman, Vice
21 President of Cardiovascular Clinical Research, SmithKline
22 Beecham Pharmaceuticals, will now present the following
23 information: a very brief review of the pharmacologic
24 profile of Coreg, a description of its hemodynamic effects,

1 and more detailed review of the principal benefits of
2 Coreg, its effect on morbidity and mortality, followed by a
3 review of its beneficial effects on clinical symptoms and
4 status. He will finish with brief comments on the safety
5 and tolerability and come concluding remarks.

6 Dr. Shusterman?

7 I might point out, as Neil walks up, all the
8 slides are numbered in the lower right-hand corner and can
9 be retrieved by number if you have any questions, comments,
10 or wish a more in-depth discussion following Neil's
11 presentation.

12 DR. SHUSTERMAN: Thank you, Dr. Powell. Dr.
13 Temple, Dr. Lipicky, members of the Cardiovascular and
14 Renal Drugs Advisory Committee, ladies and gentlemen.

15 I would like to begin by briefly reviewing the
16 pharmacologic properties of carvedilol, which may
17 contribute to its efficacy in the treatment of heart
18 failure. The drug is a nonselective beta receptor
19 antagonist and a selective alpha-1 receptor antagonist,
20 with no agonist actions at either receptor.

21 In addition, unlike other beta-blockers, the
22 drug exerts antioxidant and anti-proliferative effects.
23 These occur in concentrations similar to those that act on
24 adrenergic receptors and produce a variety of benefits in

1 experimental models of myocardial and vascular injury.

2 However, the importance of these additional properties to
3 the efficacy of the drug in heart failure remains unknown.

4 The actions of carvedilol on alpha and beta
5 receptors are responsible for the hemodynamics of the drug
6 in patients with heart failure. The first doses of
7 carvedilol produced alpha blockade, resulting in peripheral
8 vasodilatation. As a result, blood pressure falls
9 slightly, but cardiac function is usually maintained.

10 During long-term treatment, carvedilol, like
11 other beta-blockers, improves cardiac performance as
12 reflected by the increases in stroke volume and decreases
13 in right and left ventricular filling pressures. The drug
14 produces consistent decreases in pulmonary artery pressures
15 and heart rate, but with little effect in the long term on
16 systemic blood pressure.

17 In summary, the hemodynamic effects of first
18 doses of carvedilol appear to be primarily related to the
19 actions on alpha receptors, whereas the hemodynamic effects
20 of long-term treatment with carvedilol are related to its
21 actions on beta receptors.

22 The ability of carvedilol to improve cardiac
23 function has been confirmed in each of the placebo
24 controlled trials that have been carried out with the drug.

1 In all, eight studies, therapy when carvedilol, when added
2 to conventional therapy for 4 to 12 months produced a 5 to
3 9 ejection fraction unit increase in the left ventricular
4 ejection fraction, associated with the p values shown here.
5 This increase in ejection fraction with chronic treatment
6 is greater than that reported for any other drug evaluated
7 for the treatment of heart failure.

8 The improvement in ejection fraction with
9 carvedilol was related to the dose of the drug. In a
10 parallel dose response study that compared a low dose, an
11 intermediate dose, and a high dose, carvedilol produced
12 dose-dependent increases in ejection fraction after 6
13 months of treatment. The p value for this dose response
14 was 0.008.

15 This improvement in ejection fraction was
16 associated with a decrease in the chamber dimensions of the
17 left ventricle. This decrease in dimensions occurred in
18 addition to any effect that an ACE inhibitor might have to
19 diminish left ventricular size.

20 In this placebo-controlled long-term study of
21 carvedilol in patients already receiving an ACE inhibitor,
22 left ventricular end diastolic and end systolic dimensions
23 were measured at baseline, and then after 6 and 12 months
24 of treatment. Whereas both dimensions remained stable over

1 time with the placebo treatment, these decreased over time
2 with treatment with carvedilol. The p values for the
3 differences between the two groups for both measurements at
4 the two time points ranged from 0.0004 to 0.047.

5 I would now like to describe the clinical
6 trials development program for carvedilol in heart failure.
7 Carvedilol has been evaluated, as I said, in eight
8 randomized, double-blind, placebo-controlled trials. These
9 studies can be grouped into two categories.

10 First, the single-center studies, study 033,
11 BMI-01, and 035, each of which enrolled approximately 40 to
12 60 patients and maintained double-blind therapy for
13 approximately 4 months.

14 The U.S. multi-center program, consisting of
15 four studies, 239, 221, 220, and 240. These studies
16 recruited several hundred patients and lasted approximately
17 6.5 to as long as 15 months.

18 And study 223, the Australia-New Zealand heart
19 failure trial, which was the largest and longest of the
20 trials with double-blind treatment lasting outwards to 18
21 to 24 months.

22 Now, the designs of the single-center trials
23 are described on this slide. Each of the three trials
24 enrolled patients with a ventricular ejection fraction less

1 than or equal to 35 percent. With persistent symptoms of
2 heart failure despite treatment with digitalis, diuretics,
3 and an ACE inhibitor, study 033 enrolled patients with mild
4 heart failure, while study BMI-01 enrolled patients with
5 more moderate heart failure, and study 035 enrolled
6 patients with severe heart failure.

7 Again, patients were randomized to either
8 carvedilol or placebo for a treatment period of 4 months at
9 the target doses indicated here.

10 The design of the U.S. multi-center program is
11 shown on this slide. In this program patients with heart
12 failure and an ejection fraction less than or equal to 35
13 percent, despite conventional therapy, again with
14 digitalis, diuretics, and an ACE inhibitor, entered a
15 common screening period, during which an evaluation of
16 exercise performance by a 6-minute walk test was performed.

17 Based on the performance on this test, patients
18 were then stratified into one of four individual trials.
19 Patients with preserved exercise tolerance were stratified
20 to study 240. Those with intermediate exercise tolerance
21 went to either study 221 or 220, and those with the most
22 impaired exercise tolerance were assigned to study 239.

23 In all studies, after an open-label period,
24 during which patients received low doses of carvedilol to

1 determine tolerability, patients were then randomized to
2 placebo or carvedilol, up-titrated to target doses over a
3 period of 2 to 8 weeks, and then were continued on double-
4 blind therapy during a maintenance period lasting from 6 to
5 12 months. During this time, background medications were
6 to be kept constant.

7 Please note that the allocation ratios to
8 carvedilol or placebo varied in the four studies from 1 to
9 1, to 3 to 1. In three of the studies, 240, 221, and 239,
10 carvedilol was titrated to a target dose in the range of 25
11 to 50 milligrams twice daily, whereas one trial, study 220,
12 was designed as a parallel dose-response study with
13 patients being randomized to placebo or one of three doses
14 of carvedilol.

15 The occurrence of major fatal and non-fatal
16 events within each study and across the entire program was
17 prospectively monitored by a data and safety monitoring
18 board, which recommended early termination of the entire
19 U.S. program because of the finding of a favorable effect
20 of carvedilol on mortality. Early termination of the U.S.
21 program modestly affected follow-up and recruitment in
22 study 240, but had a pronounced effect on both enrollment
23 and follow-up in study 239.

24 Finally, the Australia-New Zealand trial was a

1 multi-center study which enrolled patients with heart
2 failure due to ischemic heart disease. Again, following
3 baseline evaluation, patients with an ejection fraction
4 less than 45 percent receiving a diuretic and an ACE
5 inhibitor, were randomized to either placebo or carvedilol.

6 This study had two phases. The short-term
7 phase was designed to evaluate several physiologic and
8 clinical endpoints at 6 and 12 months, whereas the
9 objective of the long-term phase was to evaluate the effect
10 of carvedilol on morbidity and mortality over 18 to 24
11 months.

12 I would like to begin the discussion of the
13 clinical efficacy of carvedilol with a review of the
14 effects of the drug on morbidity and mortality. There are
15 two reasons to do so.

16 First, the effect of any drug on morbidity and
17 mortality is of unquestioned clinical importance.

18 Second, all of the new information and analyses
19 that have been performed since the May 1996 meeting of the
20 advisory committee have focused on the effects of
21 carvedilol on morbidity and mortality.

22 When the clinical trials program with
23 carvedilol was being designed, there were good reasons to
24 think that the drug could have a favorable impact on the

1 natural history of heart failure. In experimental models
2 of heart failure, long-term beta blockade can prevent the
3 progression of heart failure when initiated early and can
4 reverse the process of ventricular remodeling when started
5 later.

6 Beta blockade has been shown to prolong
7 survival in cardiomyopathic hamsters also.

8 And furthermore, long-term treatment with beta
9 blockade has been shown to reduce the combined risk of
10 morbidity and mortality in large-scale trials with
11 metoprolol and with bisoprolol.

12 Evidence that carvedilol could reduce morbidity
13 and mortality emerged from the early single-center studies
14 with the drug. One of the single-center studies enrolled
15 high risk patients and in this study the investigators
16 performed a retrospective analysis of the effect of
17 treatment on major cardiovascular endpoints.

18 Morbidity and mortality was defined as death,
19 plus hospitalization for worsening heart failure, or
20 resuscitated sudden death. The combined risk of morbidity
21 and mortality was significantly reduced in the carvedilol
22 group, p equals 0.028.

23 Thus, based on the experimental data,
24 information from trials with other beta blockers, and the

1 results of carvedilol in the study just described, the
2 hypothesis that carvedilol had a favorable effect on
3 morbidity and mortality was developed and then
4 prospectively evaluated in the two largest placebo-
5 controlled trials carried out with the drug, study 240 and
6 220. These two trials also had the longest duration of
7 follow-up.

8 First, I will describe study 240. This slide
9 shows its design, which is typical for all of the studies
10 in the carvedilol program. After an initial screening
11 period, all patients received open-label therapy with low
12 doses of carvedilol for 2 to 3 weeks. Those who tolerated
13 6.25 milligrams twice daily were then randomized to
14 carvedilol or placebo in a 2 to 1 ratio.

15 The double-blind period consisted first of an
16 up-titration period where patients were increased to the
17 target dose, and after that by a 12-month maintenance
18 period, during which background therapy was to be kept
19 constant.

20 Of the 389 patients who entered the run-in
21 period of study 240, 23 did not complete for the reasons
22 shown at the top of this slide. As a result, 366 patients
23 were randomized, 134 to placebo, 232 to carvedilol. The
24 two groups were balanced with respect to baseline,

1 demographic, and clinical characteristics.

2 During double-blind therapy, approximately 10
3 percent of placebo patients but only 7 percent of
4 carvedilol patients failed to complete double-blind therapy
5 or were active at the time of DSMB decision to terminate
6 the U.S. program. The most important reasons for
7 withdrawal were death and worsening heart failure, and
8 these events occurred more frequently in the placebo group
9 than in the carvedilol group.

10 The primary endpoint for study 240 specified in
11 the original protocol was the combined risk of morbidity
12 and mortality. This was prospectively defined as the
13 composite of three events: first, death due to heart
14 failure, or sudden death; second, hospitalization for
15 worsening heart failure; and third, worsening heart failure
16 that was severe enough to require a sustained increase in
17 background medication as defined on this slide.

18 Several physiologic and clinical measures were
19 prospectively defined as secondary endpoints in this trial,
20 and these will be discussed a little later in this
21 presentation.

22 It should be noted that the FDA medical
23 statistical review refers to incomplete data on study
24 medication in this trial, including a reference to missing

1 data on 60 percent of patients. While study medication
2 data have always been complete since the submission of the
3 NDA, prior to May 2nd, 1996, the data were not in an easily
4 extractable form for computer analysis.

5 On that date, SmithKline Beecham delivered new
6 data sets and programs to the FDA that allowed for complete
7 electronic replication of our results. Again, I want to
8 emphasize that no medication data are missing on any of the
9 patients.

10 This slide shows the effect of carvedilol on
11 the primary endpoint of study 240. When all randomized
12 patients were included in the analysis, 21 percent of the
13 placebo group, but only 11 percent of the carvedilol group
14 experienced one or more of the three events that comprised
15 the primary endpoint. This difference reflected a 48
16 percent reduction in relative risk, significant p value of
17 0.008.

18 This slide also shows the breakdown of the
19 three events in hierarchical order, with death taking
20 precedence over hospitalization, which took precedence over
21 a change in CHF medications. As can be seen, each
22 component of the primary endpoint occurred less frequently
23 on carvedilol than on placebo.

24 The same data as shown on the previous slide

1 are displayed here as Kaplan-Meier plots using a time-to-
2 first-event analysis. As can be seen, the curves diverge
3 early and continue to separate over time. Placebo is
4 indicated in blue-green and carvedilol in yellow. Using
5 this analytic approach, carvedilol reduced the combined
6 risk of morbidity and mortality by 53 percent, with a p
7 value of 0.005.

8 To further evaluate whether the effect on the
9 combined endpoint was related to a concordant effect on its
10 individual components, the hierarchical analysis was
11 repeated twice after sequentially omitting the least
12 important components. This was done in response to a
13 specific FDA request, and these additional analyses were
14 submitted by the sponsor to the FDA since the first
15 advisory committee meeting on carvedilol.

16 The top line shows the primary endpoint as
17 defined in the protocol, and as I showed on the previous
18 slides. The second line shows the effect of carvedilol on
19 death and hospitalization. This analysis was carried out
20 by omitting the medication component. Please note that the
21 risk reduction remains stable and the treatment effect
22 remains significant.

23 This third line shows the effect of carvedilol
24 on heart failure deaths. This analysis was carried out by

1 omitting any contribution of either hospitalizations or
2 background medications. Even when more than 90 percent of
3 the events are eliminated, the effect of carvedilol
4 remained significant.

5 The analyses on this slide demonstrate that the
6 benefit of carvedilol on the primary endpoint in study 240
7 does not depend on the medication component. These results
8 and their supportive analyses demonstrate that when added
9 to conventional therapy for up to 15 months, carvedilol
10 reduces the combined risk of morbidity and mortality in
11 patients with chronic heart failure.

12 Next I want to review the results of study 223,
13 which was the second large-scale trial that prospectively
14 evaluated the effect of carvedilol on morbidity and
15 mortality. Again, this slide shows the study design and as
16 in study 240, after an initial screening period, patients
17 received low doses of carvedilol and those who were able to
18 tolerate 6.25 milligrams twice a day were then randomized
19 in a 1-to-1 fashion to either carvedilol or placebo.

20 This was then up-titrated during the first 2
21 weeks of the study until target doses were reached, and
22 after that, patients were continued on double-blind therapy
23 for a maintenance phase that extended for 18 to 24 months.

24 Please remember that the study was divided into

1 two phases, a short-term phase, which was designed to
2 evaluate the effects of carvedilol on exercise tolerance,
3 ejection fraction, and left ventricular dimensions, and the
4 long-term phase, which was designed to evaluate the effect
5 of the drug on the combined risk of morbidity and
6 mortality.

7 A total of 415 patients were randomized into
8 the study, 208 to placebo, 207 to carvedilol. The two
9 groups were well matched for most baseline characteristics,
10 except for nominally significant differences for sex, New
11 York Heart Association class, and history of angina.

12 This study was an investigator-initiated study.
13 The original protocol was written by the investigators, and
14 it did not clearly define primary or secondary endpoints.
15 However, the protocol defined specific objectives for the
16 two distinct phases of the study.

17 First, it defined the objectives of the short-
18 term phase. "Data on exercise capacity, left ventricular
19 function, and left ventricular size will be collected at
20 baseline, and after 6 and 12 months of follow-up."

21 Next, it defined the objectives for the long-
22 term phase. "Data on mortality and major morbidity,
23 including hospitalization for worsening CHF, and signs and
24 symptoms of heart failure will be collected over 18 months

1 of follow-up in all patients."

2 The two phases were quite distinct. The short-
3 term objectives were not evaluated during the long-term
4 phase, and the long-term objectives were not analyzed
5 during the short-term phase.

6 Carvedilol exerted a favorable effect on two of
7 the three short-term objectives, specifically on left
8 ventricular ejection fraction and on left ventricular
9 dimensions, but it had no effect on maximal exercise
10 tolerance.

11 Now, I want to focus the remainder of this
12 discussion on mortality and major morbidity in this study,
13 and in so doing, I want to emphasize that this information
14 has been analyzed and submitted by the sponsor to the FDA
15 since the first advisory committee meeting on carvedilol.

16 Mortality and major morbidity was defined by
17 the investigators as the main objective of the long-term
18 phase of the study. This was not only noted in the
19 original protocol, but it was specifically reiterated in
20 writing by the investigators following the completion of
21 the short-term phase.

22 Before the blind of the study was broken,
23 mortality and major morbidity was operationally defined as
24 the combined risk of all-cause mortality and all

1 hospitalizations. This was to be analyzed by a time-to-
2 first-event approach, using a log-rank test. Morbidity and
3 mortality was monitored during the trial by a prospectively
4 constituted data and safety monitoring board.

5 All patients in this study were to be followed
6 for the intended duration of double-blind therapy. No
7 patient was lost to follow-up for the analysis of
8 mortality. And in addition, no patients were lost to
9 follow-up for the analysis of hospitalizations. This slide
10 was an earlier version, and the reason for that is we have
11 now obtained complete follow-up information on
12 hospitalizations until the end of this study in all 7
13 patients. An analysis you will see today, hopefully,
14 reflects the inclusion of these new data.

15 At the end of the trial, 80 to 85 percent of
16 the patients at risk were still taking double-blind
17 medication and this proportion was similar in the placebo
18 and carvedilol groups.

19 This slide shows the effect of carvedilol on
20 all-cause mortality and all hospitalizations. As can be
21 seen, the curve diverged after about 6 to 7 months and
22 continued to separate over time. Overall, carvedilol
23 reduced the combined risk of morbidity and mortality by 23
24 percent, p equals 0.045.

1 This slide shows the effect of carvedilol on
2 the individual components of the combined endpoint. The
3 effect on mortality alone and the effect on morbidity alone
4 are concordant with the overall effect on the combined
5 endpoint.

6 Although not specified in the original
7 protocol, the FDA requested that the effects of carvedilol
8 on morbidity and mortality in study 223 be adjusted for
9 baseline covariates to account for the potential imbalances
10 in the two groups at baseline. To do so, three covariates
11 of prognostic significance were selected: NYHA class,
12 maximal exercise tolerance, and ejection fraction.

13 When any combination of these three variables
14 were included as covariates in a Cox regression model, the
15 magnitude of the risk reduction with carvedilol remained
16 extremely stable and the effect of carvedilol remained
17 significant.

18 To summarize at this point, the effect of
19 carvedilol on morbidity and mortality was prospectively
20 defined and evaluated in two studies, study 240 and study
21 223. In both studies carvedilol produced an important
22 effect to reduce the combined risk of morbidity and
23 mortality, over a follow-up period as long as 18 to 24
24 months.

1 In order to further substantiate this effect,
2 the FDA requested additional retrospective analyses of the
3 other large multi-center studies, that is, studies 221 and
4 220, recognizing that study 239 was too small and too brief
5 to produce meaningful results. Both studies 221 and 220
6 were designed to evaluate the effect of carvedilol in
7 patients with moderate to severe heart failure and had
8 virtually identical study protocols.

9 Very quickly, this slide shows the design for
10 study 221 and you will notice it is identical to study 240,
11 except that patients were randomized 1 to 1 to carvedilol
12 or placebo, and the maintenance phase was 6 months rather
13 than 12 months.

14 Of the 301 patients who entered the run-in this
15 study, 23 did not complete, for the reasons shown up here,
16 and therefore, 278 patients were randomized to placebo or
17 carvedilol, 145 to placebo, 133 to carvedilol, and the two
18 treatment groups were balanced with respect to baseline and
19 clinical demographic characteristics.

20 During double-blind therapy, almost 21 percent
21 of the placebo patients, but 14 percent of the carvedilol
22 group, failed to complete double-blind therapy. All
23 reasons for withdrawal, including withdrawals for death and
24 worsening CHF, were more frequent in the placebo group than

1 in the carvedilol group.

2 The primary endpoint for study 221 was exercise
3 tolerance. Several assessments of symptoms and clinical
4 status were specified as secondary endpoints. One of the
5 prespecified secondary endpoints was morbidity, which was
6 defined in the protocol as hospitalization for
7 cardiovascular reasons. In addition, mortality was also
8 specified in the original protocol as a safety objective
9 and was prospectively monitored by an independent
10 committee.

11 This slide shows the effect of carvedilol on
12 these prespecified analyses. When analyzed according to
13 the original protocol, carvedilol reduced the risk of
14 cardiovascular hospitalization by 46 percent and the risk
15 of death by 43 percent.

16 Although the effect on morbidity alone was
17 nominally significant, one needs to be very careful about
18 looking at morbidity alone. Since patients with the most
19 rapid or severe deterioration die before being
20 hospitalized, an analysis of morbidity alone excludes
21 patients with the worst outcome.

22 For these reasons, the FDA asked the sponsor to
23 perform an analysis of the combined risk of morbidity and
24 mortality. To ensure the robustness of these analyses,

1 three definitions were used: first, the combination of
2 morbidity alone and mortality alone as defined in the
3 original protocol for study 221; second, the combined risk
4 of morbidity and mortality as defined in study 240; and
5 third, the combination of morbidity and mortality as
6 defined in study 223.

7 This slide shows the effects of carvedilol on
8 the combined risk of morbidity and mortality, using these
9 three definitions. As can be seen, depending on the
10 definition used, the combined risk of morbidity and
11 mortality was reduced by 39 to 43 percent with carvedilol.
12 With the study 240 definition, the p value was 0.004. With
13 the study 221 definition, the p value was 0.029, and with
14 the study 223 definition, the p value was 0.019.

15 This slide shows the Kaplan-Meier curves for
16 the effect of carvedilol on the combined risk of death or
17 hospitalization for any reason. This analysis is being
18 shown graphically because it was the definition used in the
19 study 223 and it makes the fewest assumptions about the
20 specific cause of an event.

21 As can be seen, the curves diverged early and
22 continued to separate during the entire duration of follow-
23 up. Overall carvedilol reduced the combined risk by 39
24 percent, p equals 0.019.

1 Next, let us take a look at study 220, the
2 second study in patients with moderate to severe heart
3 failure. Shown here again is the design, and again, it is
4 identical to study 221, except now patients are randomized
5 to one of three doses of carvedilol rather than to a single
6 dose. Otherwise, the two protocols were identical.

7 Of the 376 patients who entered the run-in, 31
8 did not complete for the reasons shown up here, leaving 345
9 patients to be randomized to the groups as shown below.
10 The four groups were balanced with respect to baseline
11 clinical and demographic characteristics.

12 During double-blind therapy, 25 percent of the
13 placebo group but only 8 to 17 percent of patients
14 randomized to carvedilol failed to complete double-blind
15 therapy. The p value for the relation between dose and
16 completion rate was 0.008.

17 Again, as in the case of study 221, the primary
18 endpoint for this study was exercise tolerance. Several
19 assessments of symptoms and clinical status were specified
20 as secondary endpoints. One of those prespecified
21 secondary endpoints was morbidity, defined in the same way,
22 that is, hospitalization for cardiovascular reasons. And
23 mortality was also prespecified as a safety objective for
24 the study.

1 This slide shows the effect of carvedilol on
2 these prespecified analyses. When analyzed according to
3 the original protocol, the risk of cardiovascular
4 hospitalization was reduced by carvedilol by 45 percent,
5 and the risk of death was reduced by 73 percent, with the p
6 value shown here.

7 However, as stated earlier, we should be
8 careful in looking at morbidity alone because patients with
9 the most rapid or severe deterioration died before being
10 hospitalized, and an analysis of morbidity alone therefore
11 excludes patients with the worst outcome.

12 For these reasons again, we were requested to
13 perform an analysis on the combined risk by the FDA and to
14 ensure the robustness of those analyses, we performed them
15 in the exact same three ways as of study 221. That is, the
16 combination of morbidity alone and mortality alone as
17 defined in the original protocol for study 220, the
18 combination of morbidity and mortality from study 240, and
19 the combination of morbidity and mortality from the
20 Australian-New Zealand trial, study 223.

21 This slide shows the effect of carvedilol on
22 the combined risk of morbidity and mortality using these
23 three definitions. For all of these analyses, please note
24 that the effect in the three carvedilol groups has been

1 combined into a single group. As can be seen, depending
2 upon the definition used, the combined risk was reduced by
3 carvedilol from 32 percent to some 54 percent. When the
4 study 240 definition was used, the p value was .049. Using
5 the study 220 definition, the p value was .001, and using
6 the study 223 definition, the p value was .002.

7 This slide shows the Kaplan-Meier curves for
8 the effect of carvedilol on the combined risk of death or
9 hospitalization for any reason. Again, this is being shown
10 because it was the definition used in 223 and uses the
11 fewest assumptions in assigning the cause for an event.
12 Again, the curves diverged early, remained separated
13 throughout the follow-up period, and the overall reduction
14 in the combined risk was 49 percent, with a p value of
15 0.002.

16 This slide and the two that follow summarize
17 the effect of carvedilol on morbidity and mortality in the
18 major multi-center trials. This slide shows the effect of
19 carvedilol on the combined risk of worsening heart failure,
20 leading to death, hospitalization, or a need for increased
21 medications. Please recall that this was the definition of
22 morbidity and mortality and the primary endpoint in study
23 240.

24 For all three studies, the relative risks are

1 less than 1, and there is considerable overlap of the
2 confidence intervals, none of which include unity. When
3 the studies were combined to estimate overall treatment
4 effect, carvedilol reduced the combined risk of morbidity
5 and mortality by 40 percent, p equals 0.0001.

6 This slide summarizes the effect of carvedilol
7 on the combined risk of death or hospitalization due to any
8 cause, and again, this was the definition of morbidity and
9 mortality from the long-term phase of study 223. For all
10 four studies, the relative risks are less than 1, and there
11 is substantial overlap of the confidence intervals. When
12 the studies were combined to estimate an overall treatment
13 effect, carvedilol reduced the combined risk of morbidity
14 and mortality by 31 percent, again with a p value of
15 0.0001.

16 Finally, this slide summarizes the effect of
17 carvedilol on the combined risk of death or cardiovascular
18 hospitalization. This was the definition of combined risk
19 based on the prespecified definition of morbidity alone and
20 the prespecified safety objective of mortality alone in
21 studies 221 and 220. Again, for all four studies, the
22 relative risks are below 1, the confidence intervals
23 overlap, and when the studies were combined, an overall
24 estimate of the treatment effect showed by carvedilol

1 reduced the combined risk by 35 percent, with a p value of
2 0.0001.

3 In summary, carvedilol reduced the combined
4 risk of morbidity and mortality in all four studies of
5 sufficient size and duration where this could be evaluated.
6 Such an effect is of unquestioned clinical importance and
7 such consistency cannot be attributed to chance alone. The
8 effect on the combined endpoint is the result of a
9 concordant effect on the components of morbidity alone and
10 mortality alone.

11 For these reasons, we believe that the effect
12 of carvedilol on morbidity and mortality forms the
13 principal basis for the approval of the drug for heart
14 failure. However, the benefits of carvedilol extend beyond
15 morbidity and mortality, as I will now present data on the
16 drug's favorable effects on symptoms and clinical status.

17 A discussion of the effects of carvedilol on
18 symptoms and clinical status is inherently more difficult
19 than the assessment of morbidity and mortality. This is
20 because measures of symptoms and clinical status are not
21 well standardized, are subject to considerable observer
22 bias, and are accompanied by a significant placebo effect.

23 There is in fact considerable uncertainty as to
24 how to measure the effect of a new drug on symptoms and

1 clinical status. No single measure has been developed that
2 can accurately reflect the utility of a new agent. Present
3 measures assess three distinct but complementary aspects of
4 heart failure, that is, the severity of symptoms, the
5 impact of heart failure on the ability to exercise, known
6 as functional capacity, or the impact of heart failure on
7 general well-being and quality of life.

8 Each of these three aspects of the disease can
9 be assessed either qualitatively or quantitatively. The
10 qualitative measures resemble the usual interaction between
11 a physician and a patient in the clinical setting whereas
12 the quantitative measures are primarily used in clinical
13 trials. Most of these measures of efficacy were utilized
14 in the carvedilol development program.

15 With this in mind, I want to review the effects
16 of carvedilol on the placebo-controlled trials carried out
17 with the drug on symptoms and clinical status. First I
18 will focus on the three single-center studies.

19 These studies were primarily designed as
20 hemodynamic studies. Each achieved its primary,
21 prespecified endpoint, which was a measure of cardiac
22 performance. However, each trial also specified measures
23 of symptoms and clinical status as secondary endpoints.

24 The shorthand used on this slide and subsequent

1 ones expresses the results in a placebo-subtracted change
2 at study endpoint. Positive changes favor carvedilol,
3 negative changes favor placebo. Results that are nominally
4 significant at the p equal 0.05 level are highlighted in
5 yellow.

6 Despite their small size and relatively brief
7 duration, carvedilol had a significant effect on heart
8 failure symptoms in both trials in which it was measured.
9 It also had a significant effect in two out of the three
10 trials that measured New York Heart Association class.

11 In contrast, carvedilol had inconsistent
12 effects on exercise tolerance. The drug had no effect on
13 maximal exercise capacity in any of the three studies, and
14 it had equivocal effects on submaximal exercise capacity.
15 Studies 033 and BMI-01 assessed submaximal exercise
16 capacity by observing the duration of exercise at 80
17 percent peak effort, and carvedilol had a favorable effect
18 in BMI-01, but did not have it in 033.

19 Only one study evaluated the effect of
20 carvedilol on the 6-minute walk of the single center
21 studies, and in this study the effect was significant. The
22 inconsistency of the effects of carvedilol on exercise
23 tolerance was attributed to the known ability of beta-
24 blockers to attenuate exercise performance.

1 Next I want to turn our attention to the
2 effects of carvedilol on symptoms and clinical status in
3 the multi-center trials carried out with the drug. As you
4 will recall, there were five multi-center trials but I want
5 to focus your attention on four of the trials. Because
6 study 239 was terminated early and had only a brief
7 duration of treatment, I will not discuss the specific
8 results of this study, although those were presented in the
9 briefing document. Instead, I will focus on the other four
10 studies.

11 First, study 240. As you will recall, the
12 primary endpoint for this study was morbidity and
13 mortality. However, this protocol also specified a variety
14 of clinical measures as secondary endpoints.

15 This slide shows the effect of carvedilol on
16 symptoms and clinical status in this study. As can be
17 seen, carvedilol exerted a favorable effect on each of
18 these measures, and this effect was statistically
19 significant for New York Heart Association class, CHF
20 symptom score, physician and patient global assessment.

21 For all qualitative measures of efficacy, more
22 patients felt better and fewer patients felt worse with
23 carvedilol than with placebo.

24 Thus, the results of study 240 are consistent

1 with the results of the single-center trials.

2 Specifically, carvedilol improved the symptoms and
3 functional capacity of patients with heart failure, but had
4 no effect on maximal exercise capacity.

5 Next, let us proceed to study 221. In this
6 study exercise tolerance, both near-maximal and submaximal,
7 were specified as the primary endpoints, and the variety of
8 clinical measures were specified as secondary endpoints.
9 By design, these clinical measures included the same
10 measures of clinical efficacy assessed in the study I just
11 showed, 240.

12 Carvedilol had no effect on maximal exercise
13 tolerance as measured by the 9-minute treadmill distance.
14 By the protocol-specified analysis, the drug had only a
15 small effect on the 6-minute walk distance, which was not
16 statistically significant. However, this analysis excluded
17 26 patients who did not have on therapy assessments, and
18 imputed values for 23 others who did not complete the
19 study.

20 Alternate approaches to this analysis that
21 attempted to include a greater number of patients with less
22 imputation of data are shown here for your interest.

23 This slide shows the effect of carvedilol on
24 the prespecified secondary endpoints of symptoms and

1 clinical status in study 221. As can be seen, carvedilol
2 exerted a favorable effect on all measures, and this effect
3 was statistically significant for New York Heart
4 Association class, physician global assessment, and patient
5 global assessment.

6 As in the case of study 240, for the
7 qualitative measures of efficacy, more patients felt
8 better, fewer patients felt worse with carvedilol than with
9 placebo.

10 And adding these results onto the previous
11 results I have shown, we can see that they are consistent
12 with the single-center results, as well as with study 240.
13 Specifically, carvedilol improved the functional capacity
14 of patients with heart failure but had no effect on maximal
15 exercise capacity, and only small effects on submaximal
16 exercise capacity.

17 Next, I will discuss the results of study 220.
18 Recall that this was identical in design to study 221,
19 except for the number of treatment arms. In this study
20 there were three treatment arms for active drug,
21 representing three separate doses. The primary and
22 secondary endpoints here, identical to study 221, were
23 exercise tolerance, but this study was designed to evaluate
24 the significance of the observed dose response

1 relationships that compared carvedilol with placebo.

2 Because the effects of carvedilol on symptoms
3 and clinical status were not related to dose, none of the
4 primary analyses of study 220 were statistically
5 significant.

6 However, when all of the doses were combined
7 and compared with placebo, there was a parallelism between
8 the effects of carvedilol shown in study 221, which I
9 previously displayed, and the effects in study 220 for a
10 number of the endpoints. This is not too surprising since,
11 again, these two studies recruited the same types of
12 patients and had a similar design.

13 Finally, I would like to present the results of
14 study 223. You will recall that this study had two
15 principal objectives, a short-term one, based on clinical
16 and physiologic measures, and a long-term one based on
17 morbidity and mortality. Measures of symptoms and clinical
18 status were not described in the protocol but were
19 collected in the case record form.

20 Although there was a mild tendency for
21 worsening on carvedilol after 6 months, this was no longer
22 present after 12 months of treatment, and the results for
23 12 months are shown here. For all three measures, there
24 was little difference between carvedilol and placebo. In

1 part, this can be attributed to the large number of
2 minimally symptomatic patients in this study who
3 mathematically could not improve.

4 Lastly, I want to present the effects of
5 carvedilol on a measure of clinical status that was used in
6 all of the U.S. multi-center trials: the global assessment
7 of well-being. This measure requires both the patient and
8 the physician to ascertain how in general terms the patient
9 is doing compared with the patient status at the start of
10 the study, so it's a relative measure. This simple measure
11 closely resembles the discussion that normally takes place
12 between patients and physicians in an office setting.

13 Here I summarize the effect of carvedilol on
14 the global assessment using the protocol-specified
15 approach. An up arrow indicates the percentage of patients
16 who improved in a given treatment arm, and a down arrow
17 indicates the percentage who worsened.

18 In each of the three largest U.S. multi-center
19 trials, regardless of whether the assessment was by the
20 patient or by the physician, more patients improved and
21 fewer patients worsened on carvedilol compared to placebo.
22 The effect was statistically significant or nearly so in
23 all six assessments.

24 This slide summarizes the effects of carvedilol

1 on symptoms and clinical status. Carvedilol produced a
2 consistent improvement in CHF symptoms, a consistent
3 improvement in NYHA class, and a consistent effect on
4 overall well-being, but only small effects on exercise
5 tolerance and quality of life. The effects of carvedilol
6 on CHF symptoms, NYHA class, and overall well-being were
7 nominally significant in a number of trials.

8 In addition, in each of these four trials
9 carvedilol improved at least three different measures of
10 clinical efficacy. Two of these trials were single-center
11 studies, and two of the trials were multi-center studies.

12 We understand that we should be cautious in
13 interpreting an effect on a secondary endpoint that did not
14 reach significance on the primary endpoint, but we should
15 note that in all four of these studies the effect of
16 carvedilol on the primary endpoint was statistically
17 significant, or nearly so.

18 In studies 035 and BMI-01, carvedilol improved
19 the primary endpoint of cardiac function. In study 240,
20 carvedilol achieved the primary endpoint of morbidity and
21 mortality, and in study 221, carvedilol improved the
22 primary endpoint of 6-minute walk distance. This pattern
23 of consistency within and across studies is unlikely to
24 have occurred by chance alone, and supports the favorable

1 effect of carvedilol on morbidity and mortality.

2 Upon the request of the FDA, we will not be
3 presenting detailed information about the safety of
4 carvedilol because the FDA has not raised any safety
5 concerns about the use of carvedilol in heart failure in
6 the clinical trials. Full information about safety is
7 contained in the briefing document provided to the
8 committee. We do wish to emphasize the following points,
9 though.

10 First, that carvedilol was safe and well
11 tolerated in the clinical trials when used with caution,
12 when up-titration was guided by specific algorithms and
13 when investigators were fully educated about the risks. In
14 the absence of these measures, the relationship of benefit
15 to risk may be considerably altered.

16 Second, side effects are frequent during
17 initiation of therapy, but these can be managed in most
18 cases by careful titration of carvedilol and by changes in
19 the doses of concomitant medications.

20

21 Third, unlike many other drugs evaluated for
22 heart failure, carvedilol exerts no adverse effect on
23 survival.

24 In conclusion, we have demonstrated that

1 carvedilol produces improvement in each aspect of the
2 hierarchy of the evaluation of heart failure.

3 First, carvedilol has substantial effects on
4 cardiac function in patients with heart failure. Ejection
5 fraction was improved in all eight placebo-controlled
6 trials carried out with the drug and is accompanied by a
7 favorable change in cardiac dimensions.

8 Second, carvedilol produced consistent effects
9 within and across studies to improve the symptoms and
10 clinical status of patients with heart failure. This was
11 shown best on the qualitative measures of patient
12 assessment such as symptoms, New York Heart Association
13 class, and global assessment. These situations most nearly
14 reproduce the usual clinical interaction between a
15 physician and a patient.

16 And third, carvedilol produced substantial
17 effects on the unquestionably important endpoints of
18 morbidity and mortality, as shown in this summary slide.
19 These benefits are observed consistently across the
20 controlled trials carried out with the drug, regardless of
21 the definition used, and additional analyses requested by
22 the FDA confirm the robustness of this effect.

23 Therefore, based on all the data presented
24 today and the documents submitted to the committee, the

1 carvedilol SNDA meets the usual standard employed to
2 conclude that drugs are effective in the treatment of heart
3 failure.

4 Thank you.

5 DR. DiMARCO: The schedule calls for a break
6 now, but I think in view of the time, the fact that we
7 started at 2:15, we'll continue until about 4 o'clock
8 before we take a break.

9 Dr. Lipicky, do you or any members of the
10 division wish to say anything at this point?

11 DR. LIPICKY: No.

12 DR. MOYE: Can I ask a question of the FDA? Is
13 it true that the issue of medication status has been
14 resolved to your satisfaction in study 240?

15 DR. LIPICKY: That's a very complicated
16 question. I guess the short answer is yes.

17 The long answer is that, depending on what you
18 do, you see there are slightly different p values
19 associated with the analysis. Regardless of what you do
20 and what you assume, it's always got better than a nominal
21 p of .05.

22 DR. MOYE: So, regardless of what you do, the p
23 value winds up being less than .05.

24 DR. SHUSTERMAN: But Dr. Moye, the issue that

1 arose last time, whether the FDA had executable files to
2 run algorithms has been solved.

3 DR. LIPICKY: Okay, fine. Let me say, the
4 problem was that in the original data that we obtained --
5 we had all of the original data that was to run analyses
6 ourselves. The data in those files regarding the
7 medications was in our judgment not sufficiently obvious to
8 be able to decide what the basis for decisionmaking was.

9 Those files were sent. We don't think it's a
10 big issue. Did I say something wrong? And so okay, I was
11 just checking with the reviewers, and they say we don't
12 think that's a big problem.

13 DR. DiMARCO: Dr. Temple?

14 DR. TEMPLE: The reason it's not a big problem
15 is that we did an extremely conservative analysis based on
16 the small fraction of patients whose medications were
17 thought to be adequate, the result of which was to greatly
18 reduce the data set, but it was still significant at the
19 usual level, even doing that, which is very adverse when
20 you do an analysis for only about a third of the patients.

21 DR. DiMARCO: Dr. D'Agostino?

22 DR. D'AGOSTINO: Can I ask a couple of
23 questions? I wasn't here for the previous discussion so
24 you have to excuse me if I ask the same questions as were

1 already asked and clarified.

2 I have a couple of problems with the idea of
3 having as an endpoint death due to CHF as opposed to all-
4 cause mortality. You've done both. Also the
5 hospitalization. But in the analyses or in the studies
6 where you actually did do the hospitalization due to CHF
7 and the death due to CHF, could you just say some words
8 about how you decided somebody dies of CHF and
9 hospitalizations?

10 DR. SHUSTERMAN: The technical answer is that
11 the investigators coded the deaths when they occurred and
12 coded the hospitalizations. They were then reviewed
13 internally in a blinded fashion to ensure that deaths that
14 reasonably could be considered also to be CHF were not
15 excluded. But it turns out the majority of the deaths, 70,
16 75 percent, would be considered related to heart failure,
17 either a sudden death, which is why we included that
18 definition, or worsening of the signs and symptoms
19 ultimately leading to death.

20 DR. D'AGOSTINO: One of your analyses that has
21 a nice p value with it represents four deaths in one group
22 and zero in another group. I sit on the Framingham
23 committees where we try to figure out what people are dying
24 of. My sense of our imprecision would put a few of the

1 zeroes, deaths suddenly. That group would probably have
2 quite a number that might be related to CHF.

3 I like the all-cause mortality and I like the
4 hospitalization for the sort of all-cause or the CVD
5 hospitalization. Just what I am trying to clarify is I
6 don't think we should keep jumping back and forth between
7 the two because I think there are problems with the CHF
8 hospitalization and mortality.

9 DR. DiMARCO: I think Dr. Califf has a comment
10 here.

11 DR. CALIFF: I just want to stay on this line,
12 and just for understanding because I really agree with
13 Ralph and I would hope that maybe we could quickly dispose
14 of cause-specific endpoints in the discussion.

15 But just to be sure, you said they were
16 internally reviewed also. By whom, and was the internal
17 review bonded? And are the data you are presenting the
18 internal review or the investigators' call on the cause-
19 specific endpoints, both death and hospitalization?

20 DR. SHUSTERMAN: The internal review was done
21 by the medical monitors for the trials. It was done before
22 the blind was broken. And what was the last part of your
23 question?

24 DR. CALIFF: The data you presented, is it the

1 investigators' call or is it the internally reviewed call?

2 DR. SHUSTERMAN: The more conservative call was
3 used, so if the investigators excluded a death and ours
4 included it, we would include the death, or the
5 hospitalization.

6 DR. DiMARCO: Dr. Temple, you had a comment?

7 DR. TEMPLE: There is a slight problem in your
8 preference for all-cause mortality. It wasn't the
9 identified primary endpoint, so you get into a bit of a
10 box. We don't disagree with you at all, but in study 240,
11 the identified endpoint was --

12 DR. D'AGOSTINO: No. I understand that. 240
13 is 240, and we make whatever we can out of that, but we're
14 going to move to looking at mortality across these studies.

15 DR. TEMPLE: That actually helps a lot.

16 DR. DiMARCO: Dr. Borer.

17 DR. BORER: When the multi-center study was
18 stopped all the patients on placebo were offered
19 carvedilol.

20 DR. SHUSTERMAN: That is correct.

21 DR. BORER: I don't know how many of them took
22 it, and I don't know whether you followed these patients,
23 but that's going to be my question. And I understand fully
24 all the problems associated with looking at data you didn't

1 expect to look at and all that.

2 Just my own information, if you have the data,
3 it would be of interest to me to know whether a substantial
4 majority of the patients who were on placebo took the
5 carvedilol and if you followed them. And if you did follow
6 them, was there an upward break in the survival curve in
7 that previously placebo-treated group. So that it would
8 approach the carvedilol curve. Do we know that?

9 DR. SHUSTERMAN: I can tell you that greater
10 than 90 percent of the patients in both arms at the time
11 the trials were discontinued, continued on open label
12 carvedilol. We have done the analysis that you have
13 suggested. That is, look at the mortality in patients
14 previously on placebo, switched over to carvedilol.

15 As you can imagine, because it's not a
16 concurrent control, it is, I think, a sloppy analysis, but
17 the curve for those patients for mortality tracked the
18 group that started on carvedilol. That we have on a slide
19 and there it is.

20 The lowest line is placebo during the double-
21 blind trials. This is carvedilol during the double-blind
22 trials, and this line is patients previously on placebo
23 switched over to carvedilol. The numbers drop off after
24 about a year or so here when this analysis was done, so I

1 wouldn't pay too much attention to the tails, but for the
2 first part of the curve virtually overlapping the original
3 carvedilol.

4 DR. COLUCCI: If I could just add, this data,
5 this analysis was exactly as shown here, shown at the
6 American Heart Association meeting in November. The other
7 interesting line there are the patients on drug who have
8 now been followed for a median time of over 2 years.

9 DR. DiMARCO: Could you please identify
10 yourself, sir?

11 DR. COLUCCI: Wilson Colucci. I was the PI of
12 study 240.

13 So, I just wanted to amplify a little bit on
14 this data. This was an analysis undertaken by the
15 investigators and presented as an abstract at the American
16 Heart meeting last November.

17 Then to amplify further, the treatment group,
18 who have now been continued for a median treatment of over
19 2 years, have continued on a virtually identical trajectory
20 to that shown there.

21 DR. KONSTAM: And, Bill, which trials are
22 represented in these? Are these all four U.S. trials?

23 DR. COLUCCI: These are all of the patients in
24 the U.S. carvedilol trials.

1 DR. SHUSTERMAN: That is correct. This is a
2 combined.

3 DR. DiMARCO: Dr. Califf?

4 DR. CALIFF: I have a couple of questions.
5 Maybe I should go to the last one first because I don't
6 know if you have the data handy.

7 What would help me the most would actually be
8 to have the actual data for death and all-cause
9 hospitalization for all the studies that have been done.
10 It seems like it's been hard for me to follow. There's so
11 much jumping around. But if we just had all-cause
12 mortality and all-cause hospitalization with the number of
13 patients, the number of events, and the odds ratios for
14 each study and then combined, I think that would give us a
15 very nice way of looking at the data in an unambiguous way
16 that would get us out of this flipping back and forth.

17 I don't know if you have the data handy. It
18 seemed like one of the slides you showed almost had all of
19 it but not quite.

20 DR. SHUSTERMAN: The last slide showed it
21 obviously graphically in terms of the relative risk and the
22 confidence intervals as lined, but you want the actual
23 numbers.

24 DR. CALIFF: It didn't have all the studies.

1 It was missing at least one.

2 DR. SHUSTERMAN: It was only missing 239. That
3 was the small study that was terminated early and had about
4 3 months of follow-up. But if we could put the last slide
5 on.

6 DR. CALIFF: If there's a way to get at the
7 actual numbers, it would help me, and you'll understand why
8 when I ask the next couple of questions. The odds ratio
9 plots look nice but the numbers are not there.

10 Let me go ahead with the other questions while
11 you're looking for the slide.

12 This is a simple technical question I'm sure
13 you've dealt with already in terms of the left ventricular
14 function endpoints. How many missing values did you have,
15 and what did you do with the missing values in the analysis
16 in terms of people who died or people who had inadequate
17 studies, or just didn't come back?

18 DR. SHUSTERMAN: You're talking about for
19 ejection fraction?

20 DR. CALIFF: Yes.

21 DR. SHUSTERMAN: For ejection fraction, that
22 represents all patients with a baseline and an on-therapy
23 value. So, we did not impute data for patients who were
24 missing and we didn't carry forward baseline values for

1 those who didn't have an on-therapy value.

2 DR. CALIFF: The concern is obviously the
3 people who were sicker were more likely to die and not come
4 back, and so the natural outcome of a study where you had
5 deaths would be that the ejection fractions would go up,
6 since the patients who were better off were more likely to
7 be alive.

8 Of course, you have a comparison with a control
9 group, a placebo group. I'm just wondering if you did any
10 worst case kind of analyses to account for that.

11 DR. SHUSTERMAN: Well, we did not do a worst
12 case analysis on ejection fraction because we provide that
13 data to help explain the hemodynamic effect of the drug,
14 but as has been shown earlier, that's not the basis that
15 we're seeking approval for.

16 DR. CALIFF: But the same would hold for
17 symptomatic status.

18 DR. SHUSTERMAN: Well, for symptomatic status
19 we actually have done those analyses and when you do that
20 kind of effect, that is put in worst case for a patient who
21 drops out, then actually the results look better than I
22 have shown here.

23 DR. FISHER: Rob, your argument is correct.
24 People who die are more likely to have low ejection

1 fractions, but there are more deaths in the placebo arm,
2 and it was compared to placebo, which would tend to bias
3 against the active therapy --

4 DR. DiMARCO: Could you please identify
5 yourself, sir?

6 DR. FISHER: -- if you have a superior
7 survival.

8 DR. CALIFF: Lloyd Fisher. I'll identify him.
9 (Laughter.)

10 DR. CALIFF: But that's an indirect argument.
11 I'm really just asking whether you directly address the
12 problem in the analyses. It's also true that people who
13 are sicker, feeling worse, are less likely to come back to
14 get their non-invasive study.

15 I'm just asking if there were any direct
16 analyses done. It sounds like there weren't.

17 The last question is, I'm really hung up on the
18 run-in phase, and this was probably reviewed last time and
19 I wasn't here.

20 But it seems to me that our charge is to try to
21 answer the question, would we recommend this as a therapy
22 for a physician and a patient with heart failure, who
23 doesn't have the opportunity to go through a run-in phase
24 before things start to count.

1 I don't really know how to deal with that. I
2 don't know how to put a study in which all the patients
3 that had bad things happen are eliminated before you start
4 the treatment. I'm sure that you must have done some
5 indirect analyses to try to sort of take that into account,
6 but it's a bothersome thing that I hope the committee and
7 the clinicians and statisticians will help me out with.

8 And the reason it's important to me and the
9 reason I keep asking for numbers is that the differences --
10 all of the p values are small. The numbers of events are
11 also relatively small. And if you did a worst case
12 analysis, for example, and counted all the deaths and all
13 the drop-outs as attributable to the treated group, I
14 wonder what the results would look like.

15 DR. SHUSTERMAN: Before we show that slide,
16 could we hold up on that slide because I want to address
17 that question. I think you raised some really important
18 issues there.

19 The first is, the use of a run-in design is not
20 at all unusual and in fact, it has been preferred at times
21 by the FDA because it actually enhances the power of the
22 trial.

23 Of course, that leaves you with the dilemma,
24 what to do with the events during that time and you have

1 stated that. The problem there is, of course, there is no
2 control to compare against. You don't know whether to
3 attribute an event to the drug, to the patient's underlying
4 disease, or to the phase of the moon.

5 But what we have done and what we believe is
6 that the most appropriate analysis, where there is a
7 control, is from the point of randomization.

8 Nonetheless, we've done several analyses and
9 Dr. Fisher can speak to the one on mortality, where we have
10 included the run-in events, and they do not affect the
11 overall effect of carvedilol. We've done that on 240, 223,
12 and the overall mortality. I think maybe Dr. Fisher would
13 like to speak about mortality.

14 DR. FISHER: I think it's a very important
15 issue and I agree it's debatable whether there should be
16 run-in periods of mortality trials because as nice as
17 enrichment trials are in certain situations, here you worry
18 you help some people but other people you hurt. The net
19 effect is zero, but you kill off the high risk people early
20 so they're not in the trial when you randomize.

21 I thought this was going to come up last time
22 and I brought a lot of data. I don't have my data with me
23 but I can tell you the results of my analysis and then the
24 agency statisticians can check it when they get done.

1 I did a lot of analyses, and what I did was
2 compared both the overall mortality rate on carvedilol
3 during the run-in period with the carvedilol patients
4 during the trial and they were the same. Of course, you
5 don't have incredible statistical power, but there was no
6 directional trend or anything. It looked the same.

7 And looking at the very short early survival
8 curve, because that's all you have in the run-in period, it
9 looked the same.

10 So, there's no indication whatsoever that a
11 high-risk group was eliminated differentially because to me
12 that was a very important concern. And I think it
13 potentially could be very important in a setting such as
14 this, and I was surprised it didn't receive more attention
15 last time.

16 DR. MOYE: Lloyd, just to follow up. What
17 would happen if you assumed very conservatively that all of
18 the patients who died in their run-in period would have
19 wound up in the active group and all the survivors wound up
20 in the placebo group?

21 DR. FISHER: Well, it would have shifted things
22 in the opposite direction than if I had assumed they all
23 would have ended up in the placebo group and died.

24 DR. MOYE: But do you think that the p value

1 would have changed substantially from what was reported for
2 total mortality for the U.S. studies?

3 DR. FISHER: To me, Lem, to be honest, this is
4 an irrational analysis.

5 DR. MOYE: It's a very conservative analysis.
6 Whether it's irrational or not I don't know.

7 DR. FISHER: We can all agree to that.

8 I haven't done that, so I don't directly know
9 the answer to that. Maybe somebody else has. But all I
10 can tell you is I compared, as best I could, the rate and
11 there was no indication of an elevated mortality rate on
12 carvedilol during the run-in period.

13 DR. CALIFF: I'll buy that. I'm not
14 challenging that you did that. You would agree -- and I
15 sense a little uncertainty on your part -- that it's a
16 little hard to say, I'm going to give you this treatment
17 and if you make it through the first 2 weeks, then we've
18 proven that things will be better. That's not ideal.

19 But it looks like there are about 15 deaths in
20 the run-in phase. The document has a nice summary of the
21 run-in phase of each study. It looks like about 15 deaths,
22 and you could pretty well --

23 DR. SHUSTERMAN: Seven deaths in the U.S.
24 placebo controlled multi-center trials. Seven deaths.

1 DR. CALIFF: There are 4 in study 035 in the
2 run-in phase, and then there are 2 deaths in the New
3 Zealand study.

4 DR. SHUSTERMAN: That's right. Two deaths,
5 plus seven. We presented the U.S. multi-center phase and
6 the Australian-New Zealand.

7 DR. CALIFF: I actually got 9. Well, anyhow,
8 between 13 and 15 deaths.

9 DR. PACKER: This is Milton Packer.
10 Your question I think relates to whether there
11 were a number of run-in events and were they of significant
12 number, given the numerators, the total number of events in
13 the trial because it's hard to know how to make these
14 adjustments for run-in events, but if the numbers are small
15 then I guess everyone would be reassured.

16 I'm trying to get the exact numbers, but I can
17 give you something that I think is within about 10 events,
18 and we'll get the exact numbers for you in just a few
19 minutes.

20 But over all the placebo-controlled trials,
21 there were about 400 deaths and hospitalizations for any
22 cause. In the placebo group, it was 200 over 604, and the
23 carvedilol group about 190 over 903. That's a 32 percent
24 event rate in the placebo group, a 21 percent rate in the

1 carvedilol group. You have already seen the p value is
2 .00001. But we are talking about 400 events.

3 DR. CALIFF: But if we look at those who
4 dropped out in the run-in phase -- and about half of those
5 appear to be due to either death or heart failure -- that's
6 going to be about 120 to 140 additional events, divided by
7 half, maybe 70.

8 I'm not saying I know what to do with this.
9 It's just a point of discomfort. I've said enough and I'll
10 stop it now. But I hope that people on the panel will help
11 me understand how to deal with this.

12 DR. DiMARCO: Ralph?

13 DR. D'AGOSTINO: I'd like to ask another
14 question about study 223. I'm not clear on this long-term
15 follow-up piece. Were the individuals still under a
16 double-blind regimen, or was it an open-label component?
17 It's not clear to me.

18 DR. SHUSTERMAN: That's a good question. It
19 was double-blind treatment for the entire 18 to 24 months
20 of the trial.

21 DR. D'AGOSTINO: So, all of the analysis --

22 DR. SHUSTERMAN: No open-label at all.

23 DR. D'AGOSTINO: Can I ask one more question?

24 It's unfair, but let me ask it.

1 Do primary events mean nothing in the company?
2 What is the company policy when they run a study and the
3 primary events do not turn out to be significant? Is it
4 then assumed that you can ignore them?

5 This is a philosophical question, but I'm
6 trying to get a sense of how I'm to respond to these post
7 hoc and retrospective analyses in the presence of a non-
8 significant primary.

9 Could you tell me what you would do? Would you
10 multiply something, a multiplicative factor for the
11 analyses you've done? Or would you just ignore it?

12 DR. SHUSTERMAN: I'm going to ask Dr. Jim
13 Tiede, who's head of biometrics at SmithKline to address
14 that.

15 DR. TIEDE: Ralph, I'm not quite sure which
16 studies you're referring to, but if it's studies 220 and
17 221, we looked at those as more confirmatory information.
18 We had the prespecified endpoints for 240 and 223, but then
19 wanted to see if that would hold up when we looked at other
20 trials. So, it wasn't that we were ignoring the primary
21 endpoint. We recognized that we didn't achieve it. We
22 were looking just to see, did those studies provide a
23 result that was contradictory to the two primary studies.

24 DR. DiMARCO: Dr. Lipicky, do you have a

1 comment?

2 DR. LIPICKY: Milton, those numbers of 400,
3 that was for all kinds of events?

4 DR. PACKER: No cause-specific. This is the
5 most conservative, no-bias interpretation.

6 DR. LIPICKY: I just looked at studies 240 and
7 239 and for deaths, all told there were 10. A big jump to
8 400.

9 DR. PACKER: There were a lot of
10 hospitalizations.

11 DR. LIPICKY: I see, so that's in
12 hospitalizations --

13 DR. PACKER: And hospitalizations, which is the
14 -- and it's all-cause mortality and all hospitalizations.

15 DR. LIPICKY: Well, that was 10 all-cause
16 deaths I was talking about.

17 DR. PACKER: Yes. The total number of deaths I
18 believe in the U.S. program, all-cause, is 53 and in
19 Australia-New Zealand it's about 55 I believe. It's a
20 little over 100 events so that 25 percent of the all-cause
21 deaths and all-cause mortality is mortality, and 75 is all-
22 cause hospitalization.

23 DR. KONSTAM: So, could we complete the story
24 about if you want to call it a numerator of the events in

1 the run-in phase again in like terms. So, the total number
2 of deaths in the run-in phase were 9?

3 DR. PACKER: Nine. Seven in the U.S. study, I
4 believe 2 in Australia-New Zealand.

5 DR. KONSTAM: Compared to about 50 --

6 DR. PACKER: About 100 combined, 110 combined.

7 DR. KONSTAM: 110 combined what?

8 DR. PACKER: U.S. and Australia-New Zealand.
9 Deaths.

10 Just to go through it again, total number of
11 run-in deaths in all multi-center trials is 9. Total
12 number of deaths in the multi-center trials is
13 approximately 110. Total number of deaths and
14 hospitalizations -- and we're working to get the precise
15 numbers -- is between 25 and 30. Total number of deaths
16 and hospitalizations all across the same corresponding
17 analysis is in excess of 400.

18 DR. KONSTAM: I was under the impression that
19 you had done an analysis. Let's just stick to mortality
20 for a second with that worst case scenario of applying all
21 the deaths to the carvedilol group. Was that analysis not
22 done?

23 DR. PACKER: Yes, an analysis was done, and
24 showed that even if you took all the deaths and attributed

1 it to carvedilol, which would be the most conservative
2 analysis, the effect was still statistically significant.
3 The same analysis has been done for 240 and for 223.

4 DR. KONSTAM: Milton, what did it do to the
5 nominal p value?

6 DR. PACKER: .01, if I remember correctly.
7 You're taking all the events, attributing it to one
8 therapy.

9 DR. KONSTAM: All the deaths.

10 DR. PACKER: All the deaths, attributing it to
11 one therapy. .01.

12 DR. SHUSTERMAN: And we can show that. If we
13 can bring up prime 14, we have that.

14 This is the analysis if you include all deaths
15 during run-in, attribute them to carvedilol. The relative
16 risk is shown there. I can't read it quite from here but
17 maybe you can. And the p value, as Milton said, was .0108.

18 DR. CALIFF: Again, this only includes four
19 studies, it looks like.

20 DR. SHUSTERMAN: This is for the U.S. multi-
21 center program. We did it for the U.S. multi-center
22 program.

23 DR. DiMARCO: So, it doesn't include the 2
24 deaths in New Zealand and the 4 deaths in the 035?

1 DR. PACKER: 035 had 5 deaths and, again, that
2 was in favor of carvedilol. Please remember, 035 had a 2
3 to 1 randomization.

4 DR. CALIFF: During the run-in phase, Milton,
5 for 035, I think it said there were 4 deaths in the run-in
6 phase.

7 DR. PACKER: Gee, that's my study. I should
8 know, huh?

9 DR. SHUSTERMAN: I can tell you, across all of
10 the trials we have not done this analysis. We have done
11 this for the multi-center trials, and that's what you see
12 here. This counts the 7 run-in deaths against carvedilol.

13 DR. DiMARCO: Dr. Moye?

14 DR. MOYE: My understanding of protocol 223 is
15 that the primary endpoint was an exercise tolerance
16 endpoint. Do you disagree with that?

17 DR. SHUSTERMAN: Protocol 223 had two distinct
18 phases. I think that's pretty clear from the way the
19 investigators set up the trial.

20 Exercise left ventricular ejection fraction and
21 left ventricular size were measured at 6 and 12 months, but
22 morbidity and mortality was measured throughout the entire
23 18 months of the trial. In fact, none of those three
24 measures that I mentioned were ever done again after the

1 12-month point of the trial.

2 DR. MOYE: Well, I'm confused. Let me read you
3 a statement from the protocol. "The proposed study of 450
4 patients is not expected" -- I say again, not expected --
5 "to provide any reliable evidence about the effects of
6 carvedilol on survival. Several thousand patients followed
7 for several years would be necessary for the reliable
8 detection of plausibly moderate treatment benefits. Such a
9 study would be proposed if the results in this present
10 trial indicate that carvedilol was well tolerated by a
11 large proportion of the study population."

12 DR. SHUSTERMAN: That is precisely correct.
13 This was not a mortality trial, and that's a very important
14 point, and obviously was extremely underpowered to be a
15 mortality trial. We're talking about the combined endpoint
16 of morbidity and mortality, and for that the trial
17 following patients for 18 to 24 months, some 415 patients,
18 was an appropriate vehicle for that endpoint. That was the
19 purpose for the follow-up of that length and duration,
20 especially after no other measurements of status were
21 performed after 12 months.

22 So, this was not a mortality trial. The
23 protocol is totally correct. We are not bringing it here
24 as a mortality trial. But the protocol specifically said,

1 and I gave you the quote, that mortality and major
2 morbidity were to be looked at over the entire 18 months.

3 DR. MOYE: Well, again, I must say, I'm
4 confused by other statements in the protocol because they
5 seem to, from my point of view, contradict this. Another
6 statement says, "The major objectives of the study are to
7 determine the effects of this treatment on exercise
8 capacity, left ventricular function, and left ventricular
9 size after 6 and 12 months of treatment."

10 DR. SHUSTERMAN: That indeed was the major
11 objective for the short-term phase of the trial, and they
12 were measured at that time point.

13 DR. MOYE: I can find no statement in here that
14 says that a portion of the primary endpoint is for combined
15 morbidity and mortality, with a statement about the
16 definition of morbidity. I mean, to me it all seems
17 extremely vague and very general, which is very curious for
18 the statement for a primary objective. Do you disagree
19 with that?

20 DR. SHUSTERMAN: The protocol as written by the
21 investigators is vaguer than I think you or I would have
22 ideally liked to see. This was written some six years ago
23 by them, and the protocol was initiated by them also. But
24 it was clear that a long-term phase was a major aspect of

1 this trial. Just because the patients were followed for so
2 long with the express purpose. And that purpose has been
3 stated by the investigators, not only the quote that I have
4 in the protocol, but in additional communications.

5 If I could have prime slide 2. Their initial
6 short-term phase results were published in Circulation, and
7 this manuscript was submitted in January 1995.

8 Now, following completion of the short-term
9 phase of the trial, and the observation that carvedilol had
10 no adverse effect on exercise capacity or left ventricular
11 function or size, the decision was made to continue
12 treatment and follow-up of study patients with the main
13 objective of determining the effects, if any, of treatment
14 with carvedilol on hospital admission and mortality.

15 So, this is in the protocol. This was a
16 specific, active decision that was made for the long-term
17 purpose of the trial.

18 If I could have the next slide, please.

19 DR. MOYE: Just a second, please. If I read
20 this right, the decision was made to continue -- and please
21 tell me if I'm wrong. The decision was made after the
22 trial started to continue to the long-term follow-up. Is
23 that right?

24 DR. SHUSTERMAN: The decision was made to not

1 stop the trial, to allow it to continue for 18 to 24
2 months. It was pre-written into the protocol that they
3 would look, and if there was an adverse effect on the 6 and
4 12 months, that the protocol could be stopped. So, the
5 protocol from the start was 18 months with the ability to
6 stop it if there was something bad happening.

7 DR. MOYE: But there was no stated endpoint at
8 18 months, no well-defined endpoint?

9 DR. SHUSTERMAN: Yes, if we could have the next
10 slide. This is the correspondence with the principal
11 investigator in the trial, and the definition of the
12 endpoint mortality and major morbidity is shown here. The
13 definition that we adopted for this outcome was death from
14 any cause, or hospital admission for any cause, during the
15 period between randomization and the end of follow-up.

16 And secondly, when was this decision made? The
17 decision to use this global index of mortality and major
18 morbidity was made prior to unblinding the data on these
19 outcomes.

20 DR. MOYE: It was made after the trial was
21 started, but prior to unblinding.

22 DR. SHUSTERMAN: After it started, before it
23 was unblinded. Based on what was said in the protocol
24 about mortality and major morbidity.

1 DR. MOYE: Okay. Well, then would you have any
2 response to the criticism that the investigators had a
3 sense of how things were going and therefore tailored their
4 definition for morbidity based on their sense for the
5 direction of the data?

6 DR. SHUSTERMAN: Well, I would say that if they
7 used a cause-specific definition, Dr. Moye, but here they
8 picked the broadest, least-biased, most assumption-free.
9 All deaths, all hospitalizations. It didn't matter what
10 they were admitted to the hospital for. So, I think that
11 has the least bias in terms of being influenced by anything
12 they knew during the trial.

13 DR. PACKER: And then this decision to go
14 forward after the completion of short-term phase is
15 specifically mentioned in the original protocol.

16 Lem, the decision to go forward with the long-
17 term phase was specifically mentioned in the original
18 protocol. The original protocol said that data on
19 mortality, major morbidity would be collected for 18
20 months, extended by a protocol amendment to 24 months.

21 Then later on in the protocol it says that
22 decision would hold unless at the completion of the short-
23 term phase there was an adverse effect on the exercise
24 tolerance or LV chamber-size dimensions, ejection fraction

1 measured during the short-term phase.

2 Everything you've seen here was prespecified in
3 the original protocol.

4 DR. MOYE: Except for the definition of
5 morbidity. Right?

6 DR. PACKER: I think that if you and I would
7 recognize that the definition of mortality and major
8 morbidity needs to defining in this protocol, because it is
9 not clear from the protocol what it is, what we can be
10 reassured by is, one, they used the broadest, least-biased
11 definition possible. And two, they defined it before they
12 had any knowledge of any of the treatment effects before
13 the blind was broken.

14 I think it's perfectly consistent with the way
15 the clinical trials are run. If there is anything vague in
16 the protocol that needs defining, you define it up front,
17 you define it in the least-biased way possible, and you
18 define it before you break any codes.

19 DR. MOYE: The message I get from you, then,
20 not to belabor this, is that the decision for a follow-up
21 study was made before the trial started, but the decision
22 as to the composition of the morbidity endpoint was not.
23 But it was made before the results were unblinded.

24 DR. PACKER: The fact that there was such an

1 endpoint for the long-term phase was prespecified in the
2 original protocol. The precise definition of what
3 morbidity/mortality would be was made before the blind, as
4 you have said, after the original protocol, but I think
5 that it was made quite fairly. It's the broadest
6 definition of morbidity and mortality one can think of.

7 DR. DiMARCO: I'm glad you both agree.

8 Dr. Borer?

9

10 DR. BORER: I don't want to belabor the run-in
11 phase mortality issue. You've been very forthcoming about
12 the data and the analyses that you did to try to deal with
13 this, but I would like to know more precisely what kind of
14 analysis was done. The primary outcome analyses were time-
15 varying analyses, and these events occurred before time
16 zero.

17 What did you do? Add all the patients from the
18 run-in phase who died as carvedilol patients and assume
19 they died at time 0? Or was some other kind of analysis
20 performed?

21 DR. SHUSTERMAN: It was a time-to-event
22 analysis but instead of starting the clock, so to speak, at
23 the point of randomization, it was started at the point of
24 the very first dose of carvedilol during the open-label

1 period for all of the patients. Patients who died were
2 attributed to carvedilol. Patients who lived and went to
3 placebo were attributed to placebo. So, it was from the
4 very first dose.

5 DR. BORER: I see. Thank you.

6 DR. KONSTAM: And what's the statistical test?

7 DR. SHUSTERMAN: Log-rank test. That was a
8 Kaplan-Meier curve.

9 DR. DiMARCO: Dr. Califf?

10 DR. CALIFF: Again, I know we are belaboring
11 this, but that's been done for all of the trials with all
12 of the patients. Has it or has it not?

13 DR. SHUSTERMAN: For deaths it has not been
14 done for all of the double-blind trials.

15 DR. CALIFF: What about death and all-cause
16 hospitalization?

17 DR. SHUSTERMAN: But it has been done for the
18 U.S. multi-center program, which was the major component of
19 all of the trials.

20 DR. DiMARCO: This is 4:05. We'll take a 10-
21 minute break now and reconvene at 4:15.

22 (Recess.)

23 DR. DiMARCO: I'd like to get started. Before
24 I poll the committee and ask if there are any additional

1 questions, I'd like to ask the division if they have any
2 questions for the sponsor.

3 DR. LIPICKY: No.

4 DR. DiMARCO: Would any of the reviewers like
5 to say anything at this point? The medical or statistical
6 reviewers?

7 DR. D'AGOSTINO: I want to make a comment. Oh,
8 you're talking about the FDA reviewers.

9 DR. DiMARCO: The FDA reviewers.

10 DR. D'AGOSTINO: I would think that it's
11 important to hear one of the FDA people make a
12 presentation. They have quite a different spin on some of
13 these data. We could pick it up on our own, but I think
14 it's important to hear them say something.

15 DR. RODEN: While people are coming to the
16 microphone, can I ask what kind of criteria people used to
17 decide --

18 DR. DiMARCO: Dan, why don't we do the FDA
19 reviewers first and then we'll get to your question.

20 DR. STOCKBRIDGE: I'm Norman Stockbridge, FDA.

21 I don't have anything new to offer on the basis
22 of what we heard this morning. I think you have our
23 reviews and know what our biases are here. If you have
24 specific questions that you want to ask us, we can

1 certainly respond to that.

2 DR. DiMARCO: Rob?

3 DR. CALIFF: Maybe you could just say a few
4 words about your assessment of death and all-cause
5 hospitalization, and your view about the run-in phase and
6 analyses that you did on that.

7 DR. STOCKBRIDGE: The issues about run-in
8 phase, I think we were fairly satisfied that the point
9 estimate one has of the mortality rate specifically during
10 the run-in phase was not much different from what you saw
11 during the trial. So, it wasn't like there was a large
12 effect, and a lot of people who were at risk of dying as a
13 result of exposure to the drug got filtered out through
14 that. I think we were fairly satisfied with that.

15 We were also satisfied, I think, that there was
16 no large rebound effect associated with coming off of the
17 drug and going into the placebo group. The early mortality
18 rate in the placebo group was not unusually high. I don't
19 believe we have done any analysis that tried to look at
20 death plus hospitalization the same way. Perhaps we
21 should.

22 DR. DiMARCO: Ralph?

23 DR. D'AGOSTINO: I would like to ask some
24 questions, trying to make a judgment from the presentation

1 we just had and what I see in the review. For example, in
2 study 223 with the phase 2, there were three primary
3 endpoints in phase 1. One of them I guess was
4 statistically significant, the other one clearly wasn't,
5 and the third one was sort of marginal, which would bump
6 up. But then there's the phase 2 that comes in, where
7 there is this mortality and morbidity.

8 I think it's very important to get a sense of
9 what we think about that level of significance that's
10 produced. Would you let it go as it stands, or are you
11 suggesting that it should be --

12 DR. STOCKBRIDGE: I have a great deal of
13 trouble finding the words in the protocol that identify a
14 long-term endpoint for this trial. And that is the only
15 document that we have had, we have seen, that addresses
16 what the endpoints in that trial might be. I believe that
17 the Australia-New Zealand group had an interest in
18 monitoring safety through an extended period during that
19 trial, apparently for the purpose of considering a
20 definitive trial later on.

21 I think that if there had been a potential
22 basis for approval in a primary endpoint that was
23 identified from the short-term phase, I think they would
24 have been horrified to have had that taken away from them

1 because of some adjustment for multiple endpoints,
2 including the long-term phase. I don't think that was what
3 their intent was at all.

4 DR. D'AGOSTINO: Can I ask a couple more
5 questions?

6 In study 240, where the combined endpoint was
7 quite significant, the significance that's falling apart if
8 you remove the medication, in particular, when you look at
9 just straight mortality, this CHF mortality, you only have
10 4 versus 0 deaths.

11 I guess I'd like some sort of statement about
12 or some discussion about how one should look at that
13 medication. I started off understanding that 240 was a
14 study which everybody thought was quite nice, and the more
15 I looked at it, the more problems I had with it. I'd like
16 to hear your view on that.

17 DR. STOCKBRIDGE: The FDA reviewers never did
18 an analysis that was exactly the same as what the sponsor
19 did. In the first place, the only analyses we did were
20 time-to-first-event. The original protocol called for an
21 analysis that just simply counted events. The original
22 protocol called for components of that endpoint which were
23 cause-specific mortality, and cause-specific
24 hospitalization. The FDA reviewers never looked at cause-

1 specific hospitalization or cause-specific mortality.

2 What we analyzed was all-cause mortality and
3 all-cause hospitalization in that, and however you do that,
4 it is still true that the p value floats up by a factor of
5 about 10 if you drop the medications component.

6 DR. DiMARCO: Dr. Borer?

7 DR. BORER: You raised what sounds to me like
8 sort of a critical point a couple of minutes ago, and I
9 guess we'll need a response from the company about this.
10 But if indeed the purpose of counting deaths and
11 hospitalizations for 18 to 24 months was to monitor safety
12 and be able to make a safety statement, rather than to do
13 an analysis for efficacy, the importance -- I hesitate to
14 use the word "significance" because I think it's wrong
15 here, but the importance of any conclusions based on that
16 analysis would lose a great deal to me I think.

17 Once you said it, it reminded me of one of the
18 slides, describing study 220, where we were told that
19 mortality was a prespecified endpoint. But it was actually
20 prespecified as a safety assessment. I'm sure it was
21 prespecified that deaths were going to be counted to make
22 sure the drug was safe, but that's different from a
23 prespecified efficacy endpoint that you build an analysis
24 around.

1 DR. STOCKBRIDGE: None of the U.S. trials have
2 a protocol that specifies mortality or mortality plus all-
3 cause hospitalization, some combination of those, as a
4 primary or secondary endpoint.

5 DR. BORER: The point I was making was that it
6 does sound as if there's some similarity between the
7 prespecification of mortality as a safety issue in one of
8 the U.S. trials and perhaps the intent to look at mortality
9 and morbidity in 223 as a safety issue. I'd want to know
10 from the company whether that's what was done.

11 DR. PACKER: Jeff, the investigators made clear
12 that their intent was to look at a reduction in the
13 combined risk of morbidity and mortality. That was made
14 clear not only in the original protocol but also made clear
15 in the January 1995 decision to go forward with the long-
16 term phase. Remember, the protocol specifically said that
17 unless something bad happened on the physiologic and
18 clinical endpoint, that they would make a decision to go
19 long-term.

20 At that time they said that they were going
21 long-term to look for a reduction in morbidity and
22 mortality. It never looked at any of the data and so they
23 were actually going for this.

24 Now, their desire was to do a mortality trial,

1 not to do a morbidity/mortality trial. They were doing a
2 morbidity/mortality trial to hopefully get someone to say
3 they were going to do a mortality trial.

4 So, the protocol says that their hopes are
5 eventually to do a mortality trial, but what they
6 prespecified was the hypothesis that carvedilol would
7 reduce the combined risk of morbidity and mortality.
8 There's actually a considerable amount of correspondence
9 and material in writing to indicate that.

10 DR. DiMARCO: Do both Dr. Temple and Dr.
11 Lipicky want to make comments?

12 DR. TEMPLE: To some extent this is, I think,
13 being made more complicated than it needs to be. It's
14 perfectly obvious by now that there is nothing in the
15 protocol for the 223 study that nicely, neatly says, my
16 primary endpoint for the second phase is X. If there were,
17 we wouldn't have had to be discussing it so long.

18 I think what the company is arguing, that you
19 can deduce what it was from these various things, from the
20 statement in the publication and so on.

21 My guess is it's not going to get any better
22 than that and you sort of have to decide whether you
23 believe that's persuasive or not because the usual kind of
24 statement just isn't going to be there.

1 But I was interested in knowing why Dr.
2 Stockbridge particularly thought that they were doing it to
3 find out if it was lethal because the phrases that were up
4 there didn't seem to be saying that, but you might have
5 some other reason for thinking that.

6 Before you answer, it's important -- probably
7 everybody knows this already but I want to be sure -- to
8 distinguish between an endpoint that includes death and a
9 mortality endpoint. It's very clear that there was no
10 mortality endpoint in the U.S. trials, but there were
11 endpoints that included one or another kind of death along
12 with other things. So, it's not that death was
13 uninteresting. It's that they weren't trials to find a
14 mortality endpoint specifically.

15 Then the third thing that's worth noting is,
16 they tended to look at cause-specific stuff and we tended
17 to ask them not to because we're suspicious of the ability
18 to classify things properly. So, both endpoints were shown
19 and you can try to decide what that means. But they were
20 looking for some secondary endpoints at some of these
21 mortality/morbidity things in trials.

22 But before Dr. Stockbridge goes away, I think
23 it's important to pin down what in there would make one
24 think that they really weren't looking for a benefit at all

1 because that would be very troublesome.

2 DR. LIPICKY: Norman can answer that, but I
3 would like to also, since opinion was asked for.

4 I know that during our discussions with the
5 sponsor setting up the development program, the only
6 interest was to show there was no adverse effect on
7 mortality. That is the only thing we ever talked about.
8 That there was to be an expected beneficial effect on
9 mortality was not in the cards. It was to get a point
10 estimate to show that symptoms would be better in some
11 fashion and there would be no adverse effect on mortality,
12 or not a very large one.

13 I guess I could have planted that idea in
14 Norman's mind.

15 The second part of it is, as you read through
16 the protocol, boy, if anyone can read through that 223
17 protocol and come to the opinion that there was hypothesis-
18 testing going on looking for a benefit, they've got a
19 really good imagination.

20 So, then you put that together and you say,
21 well, they're interested in seeing what happens long-term.

22 I have a question to ask. Those letters that
23 were shown up here, when were they written? After the
24 study was completed, before the analyses?

1 DR. SHUSTERMAN: The letter I quoted was
2 written and communicated to us when these results came out
3 in The Lancet, which is in the last week. But the same
4 statements are in The Lancet publication.

5

6 DR. LIPICKY: That's fine.

7 So, the first that anybody knew anything that
8 was even close to some written-down intent was after The
9 Lancet publication was published?

10 DR. PACKER: That's not true, Ray. These were
11 specifically outlined in the investigator's publication in
12 January 1995, when they completed the analysis of the
13 short-term phase, and in that publication said that not
14 having any adverse effect in the short-term phase, as
15 specified in the original protocol, the investigators are
16 now continuing the trial for the main objective of looking
17 at the hypothesis that carvedilol reduces morbidity and
18 mortality. That was in January of 1995, before any blind
19 for morbidity and mortality was broken.

20 DR. LIPICKY: Only the short-term part. Is
21 that right?

22 DR. PACKER: Right. And the investigators were
23 not privy to any information about morbid or mortal events
24 that occurred in the study.

1 DR. DiMARCO: Cindy?

2 DR. GRINES: I've been reviewing this protocol,
3 and it mentions twice in the protocol that they actually
4 propose to perform a mortality trial if there's any
5 plausible moderate treatment benefits. So, I can't tell
6 from this protocol that they were expecting to see an
7 increase in mortality because it's twice mentioned that
8 they wanted to eventually do a large mortality trial.

9 DR. LIPICKY: I would like to add one more
10 comment to the opinion business.

11 I think we missed in our first review the
12 importance of the run-in period and how that might
13 influence things, and I'm differing a little bit with what
14 Dr. Stockbridge said in that I think we missed this run-in
15 business because the major attention was paid to the post-
16 randomization process. We were not convinced that it was
17 an effective therapy on the basis of post-randomization
18 analyses, so we didn't look for much more from the vantage
19 point of what would the design of the trials mean for
20 approvability.

21 DR. KONSTAM: So, what's your feeling about it
22 now?

23 DR. LIPICKY: Well, I think we missed it and I
24 certainly am thinking about it for the first time.

1 DR. KONSTAM: Based on the data that you've
2 seen.

3 DR. SHUSTERMAN: Regarding the run-in phase,
4 could we have backup slide 3 please because I think this is
5 germane to this discussion.

6 DR. PACKER: There are actually two backup
7 slides. That's the first one.

8 It's not unusual to have trials that have run-
9 in phases. In fact, I think such run-in phases have been
10 actually advocated by FDA. An example of a trial that has
11 a run-in phase, for example, is the SOLVD treatment trial.
12 What we did in this slide was just to compare on the left
13 the run-in events corrected for time in the SOLVD treatment
14 arm with the run-in events in the U.S. carvedilol arm. As
15 you can see, the event rates during these two periods are
16 pretty similar to each other.

17 As Dr. Stockbridge has emphasized, he didn't
18 see any evidence for an excessive increase in the events
19 during this run-in period. This diagram would confirm his
20 impression. He didn't find any excess after randomization.
21 The event rate during the run-in was similar to the event
22 rate post-randomization.

23 DR. LIPICKY: Are you talking about deaths?

24 DR. PACKER: I'm talking about deaths.

1 DR. LIPICKY: There were very few deaths. So,
2 the fact that someone couldn't find anything in the run-in
3 phase is no big surprise.

4 DR. PACKER: Deaths are pretty serious.

5 DR. LIPICKY: But there weren't very many. The
6 number were not very many.

7 DR. PACKER: Well, that's because there was --

8 DR. LIPICKY: So, if you look at it per trial,
9 you will not --

10 DR. PACKER: No, no. This is not per trial.
11 This is for the entire program.

12 DR. LIPICKY: What did Dr. Stockbridge say?

13 DR. PACKER: Sorry?

14 DR. LIPICKY: You were commenting on Dr.
15 Stockbridge's comment, and was his comment on all of the
16 data in all of the trials or was it a trial-by-trial
17 comment?

18 DR. PACKER: I guess we would have to ask him.

19 DR. STOCKBRIDGE: I suppose I could have pulled
20 out the primary review and looked at this again, but I
21 didn't.

22 I believe that what we looked at in terms of
23 the run-in period was the mortality in the U.S. experience,
24 the four major trials. We looked at all of the deaths that

1 occurred during those few weeks.

2 DR. LIPICKY: And that was a total of 12?

3 DR. STOCKBRIDGE: Yes. Well, it was something
4 like that.

5 DR. PACKER: It was seven events.

6 DR. LIPICKY: And you didn't find anything in
7 that signal, and that means something? Come on.

8 DR. PACKER: Ray, what can you find without a
9 control group? What is findable in the absence of a
10 control group?

11 DR. LIPICKY: Nothing but you were saying we
12 didn't find anything, and I'm just trying to emphasize the
13 fact that that was a non-statement.

14 DR. PACKER: But it's quoting Dr. Stockbridge's
15 statement of a few minutes ago.

16 DR. MOYE: But you can bound it. It sounded
17 like that if you assumed the worst case --

18 DR. PACKER: Can we have the next slide please?

19 DR. MOYE: -- then the p value still winds up
20 being fairly small.

21 DR. CALIFF: Don't leave the slide yet.

22 DR. MOYE: Now, if the concern is not mortality
23 but morbidity and mortality, what then happens?

24 DR. CALIFF: Can I just make a comment about

1 this slide? I'm not as convinced as Milton yet. Again, I
2 just want to keep pushing the worst case here to set that
3 boundary, but the underlying mortality in the carvedilol
4 trials is about half of what it is in the SOLVD trial. So,
5 one would expect the run-in phase mortality to be lower I
6 would think.

7 In addition, we've already learned I think that
8 the U.S. experience had a lower run-in mortality than the
9 trials that have been excluded. As you said, Milton, there
10 were four in your study and the New Zealand had another two
11 deaths.

12 So, I think we need to see all the data from
13 all the studies, and this doesn't, to me at least, provide
14 a convincing case that there's not -- it's convincing
15 there's not a huge problem. It's not a lethal problem.
16 It's not a terrible problem, but I think it is an issue
17 that needs to be sorted out.

18 DR. PACKER: Rob, in the spirit of being most
19 conservative, let me just say that it is true that you
20 might expect perhaps the event rate to be lower if
21 carvedilol was exerting an effect. But remember, this run-
22 in period, this 2, 3, 4 weeks, the carvedilol curves don't
23 separate for 3 to 6 months. So, you're not going to see a
24 beneficial reduction in a run-in period of only 2 to 3

1 weeks in duration.

2 DR. SHUSTERMAN: And they only received the
3 lowest dose.

4 DR. PACKER: And they only received the lowest
5 dose during this period of time.

6 DR. CALIFF: I'm making a very different point
7 which is that the underlying mortality in the -- it's a
8 lower risk population at a lower risk of death, and
9 therefore in the run-in phase, you would expect .25 or .20
10 or something to be consistent with what you see in the rest
11 of the trial.

12 DR. PACKER: Why would that be?

13 DR. CALIFF: Because you have patients with a 5
14 percent risk of dying at 6 months compared to patients with
15 a 10 percent risk of dying at 6 months.

16 DR. PACKER: Rob, if I can focus your attention
17 on the bottom of this slide. The actual event rate at 6
18 months in the U.S. carvedilol/placebo arm -- and don't
19 forget almost all of these patients, more than 95 percent,
20 were getting ACE inhibitors. It's exactly what was
21 observed in the SOLVD treatment arm when patients were
22 getting an ACE inhibitor. So, in fact, the evidence is
23 rather striking that these patients are a similar risk.

24 DR. KONSTAM: But it's a little lower than in

1 the SOLVD placebo arm, which is what Rob is saying. It is
2 a different baseline population, and it may well be that
3 it's different because they're on ACE inhibitors. So, it
4 is a little bit different.

5 But, Rob, I think the magnitude of this is real
6 small. If it's 7 deaths, okay. So, maybe it's a couple
7 one way or the other. I think the issue really is what's
8 the worst case scenario and the worst case scenario is that
9 all 7 deaths go over to carvedilol. I guess that's the
10 analysis that we saw.

11 DR. PACKER: Can I have the next slide?

12 Rob, this is the best we can do to address your
13 request in the short period of time available. This shows
14 the five multi-center trials. You can see the deaths in
15 run-in and then the deaths after randomization. Placebo is
16 on the left and carvedilol is on the right. I think you
17 can feel comfortable that if you took all of the deaths in
18 the run-in period, the difference between 9.9 -- these are
19 crude ratios. Please forgive us. These are not time-to-
20 first-event analyses. If you took the .55 carried over to
21 carvedilol, I'm not certain we would be having much of an
22 impact on the delta in mortality.

23 I agree that it would be important, Lem, to
24 look at this for mortality and hospitalization. It's just

1 not possible to do that right this minute. It's easy to
2 get the mortality data. It's hard to get the
3 hospitalization data.

4 DR. DiMARCO: Dr. Roden, did you have a
5 question?

6 DR. RODEN: I had a couple of questions.

7 One is perhaps to Dr. Lipicky and Dr. Temple.
8 I've seen the list of questions, but I want to know what it
9 is we're being asked. Are we being asked to decide whether
10 carvedilol reduces mortality, or are we being asked whether
11 it's a useful drug in the treatment of patients with heart
12 failure? So, that's one question.

13 Then the other question I had for Milton or
14 someone over there, and that is mortality is easy.
15 Hospitalization seems to me a very, very mushy endpoint
16 depending on physician preferences. I'd like some sense of
17 how you think those kinds of decisions were made and
18 whether it is conceivable that because these patients are
19 part of a trial in which endpoints were desirable, that
20 there's a bias toward increasing the number of
21 hospitalizations.

22 DR. PACKER: It's very hard to address that
23 last question because I would like to think that the
24 patients who are in a trial -- and I think you would share

1 this view -- in general tend to get a much more vigilant
2 type of care than patients who are not in a trial. This is
3 regardless of whether they get placebo or active therapy.

4 DR. RODEN: Well, hospitalization as a sort of
5 endpoint may change the way people approach that.

6 DR. PACKER: No, I understand. I think that in
7 general when one looks at either mortality or combined risk
8 of morbidity and mortality, in general the event rates are
9 lower than the trial predicts. There are lots of reasons
10 why. It's a lower risk patient population, or perhaps
11 because investigators really are more vigilant. So, in
12 general, the hospitalization rates are lower than expected
13 because of that. It's hard to distinguish between that and
14 other factors that you might identify.

15 There's no doubt that the most unbiased,
16 clinically important endpoint in the measurement of heart
17 failure -- and by the way, measurement of any disease -- is
18 mortality. But I think that ranking right underneath that
19 is mortality and morbidity.

20 That has certain advantages. One is it tells
21 you a little bit more about what the drug is doing to the
22 progression of the disease because hospitalization is an
23 intermediate endpoint. Two, hospitalization is easy to
24 quantify. It's objective.

1 DR. RODEN: So you say.

2 DR. PACKER: Three, biases hopefully should be
3 randomizable out between placebo and active therapy. I
4 share Ralph's concern about cause specificity which is why
5 just a week ago I emphasized in an editorial in the New
6 England Journal that one really needs to focus on all-cause
7 mortality and all-cause hospitalization as a combined
8 endpoint because that gives you the highest degree of
9 comfort that what you're looking at is is not subject to
10 biases. It is right underneath mortality as the most
11 important thing you can measure in heart failure.

12 DR. DiMARCO: Dr. Temple?

13 DR. PACKER: And by the way, that's why the
14 analysis on carvedilol on all-cause mortality and all
15 hospitalizations across studies is so important.

16 DR. TEMPLE: Just a little history and theory.
17 We've certainly accepted reduction in cardiovascular
18 hospitalization rates as a legitimate endpoint. That's
19 what SOLVD Prevention showed.

20 We've said repeatedly that it's cleaner and
21 easier to understand if you look at all-cause anything, but
22 that doesn't mean that it's not sometimes reasonable to
23 look at cause-specific events. What you have to do is
24 protect yourself against bias and make sure there's an

1 independent group that's blinded that makes the
2 interpretations. It would be I think a real stretch to say
3 that one mustn't do that, however.

4 But I wanted to go back to the previous
5 discussion. Dr. Stockbridge was initially satisfied that
6 nothing funny was going on in the pre-randomization period
7 by looking at overall rates. Dr. Califf has raised the
8 question that there's a simpler way to do this and a more
9 conservative way to look at this by simply attributing all
10 of those events to the drug even though they happened
11 before randomization. We will obviously eventually be able
12 to see that.

13 I want to be sure we understand what point is
14 being made because we've looked at both pre-randomization
15 deaths and pre-randomization deaths plus hospitalizations.

16 The main endpoint on which the company is
17 hoping, at least potentially, to rely is not the deaths.
18 It's the deaths plus hospitalizations. So, if one wants to
19 look at the robustness of that finding, then it's the death
20 plus hospitalization issue that needs to be looked at, and
21 they have apparently done that for the U.S. multi-center
22 studies, but that leaves some things out and it shouldn't
23 be very difficult, even if they can't do it right now, to
24 get the rest of those data.

1 So, do I understand that that's the main
2 question that's being raised? You'd like to see an
3 analysis that conservatively attributes all of those to the
4 drug as if none of them would have happened in a placebo
5 group. Is that correct?

6 DR. CALIFF: That's my question. It may not
7 reflect anybody else's interest.

8 DR. MOYE: I agree. I think that's critical
9 here.

10 DR. TEMPLE: There is a second question and
11 it's important. We know from the CAST, for example, which
12 used a screening period and had lots of deaths during the
13 pre-randomization period, that at least for moricizine the
14 action was all in the pre-randomization period. The
15 mortality attributed to the drug was all in the screening
16 period, and by the time you got into the screening period,
17 it wasn't nearly as bad to be on moricizine because you had
18 killed off all the susceptibles.

19 So, looking for excess deaths, people
20 hypersensitive to a beta-blocker, is also a reasonable
21 question, but my impression is that what Dr. Stockbridge
22 did reassured him on that question that people were not
23 dying at a terrible rate during that period.

24 So, I just wanted to be sure I got the two

1 questions separated and know what everybody wants to find
2 out.

3 DR. DiMARCO: Dr. Konstam?

4 DR. KONSTAM: I'd like to ask two questions.
5 I'd like to ask Milton, and maybe other people in the
6 audience who were investigators could comment on it too.

7 Following up Dan's point with regard to
8 potential bias, I'm a little concerned about heart rate
9 effects, and I think that hospitalization is subjective in
10 the sense that it requires a decision by the clinician, as
11 certainly does change in medication. I know if I have a
12 patient whose heart rate is 110, I'm much more likely to be
13 worried about that patient than somebody whose heart rate
14 is 80. It's one of the things that consciously or
15 unconsciously goes into my mind as a clinician.

16 I wonder if you can comment on the likelihood
17 that that biased these endpoints that required subjective
18 judgment.

19 DR. PACKER: Well, that question, I think the
20 issue of potential bias comes up with any beta-blocker for
21 any indication other than mortality. Taken to an extreme
22 -- and I know you're not suggesting that -- you would say
23 that the only endpoint you would believe in a beta-blocker
24 trial would be mortality because any other endpoint could

1 conceivably be influenced by a physician who may be
2 influenced by what he sees as a change in heart rate.

3 What's gratifying about what you see in the
4 carvedilol program, for reasons that are not clear, is that
5 in the analyses that have been done to date on a variety of
6 endpoints -- and I don't think it has been done on
7 hospitalization, by the way -- there doesn't appear to be
8 any difference in the delta heart rate in the patients who
9 had or did not have an event. In other words, it wasn't as
10 if the investigators systematically hospitalized all the
11 patients with high heart rates.

12 DR. DiMARCO: I think what Marv was saying is
13 that if the patient presents with worsening heart failure
14 and a high heart rate, they're more likely to be
15 hospitalized because they may appear sicker.

16 DR. PACKER: I think, John, there's a
17 likelihood that the bias would have been in the opposite
18 direction because if an investigator could determine what
19 the patient was on by looking at their heart rates -- and
20 there's evidence from these trials that they could not
21 determine who was on placebo or carvedilol by an individual
22 measurement of heart rate. So, let me emphasize that. But
23 if they could, they might be more likely to hospitalize
24 someone who they thought was on a beta-blocker.

1 DR. KONSTAM: I was thinking pretty much what
2 John said, that I don't think it's so much an issue to me
3 of the investigator guessing what they're on as much as
4 that heart rate per se is one of the things that good
5 clinicians -- that enters into their decisionmaking
6 consciously or unconsciously. I'm a little concerned about
7 that as a bias in the data set.

8 DR. WEBER: But you're saying, Milton, that in
9 fact did not place.

10 DR. PACKER: That did not take place.

11 DR. DiMARCO: What I'd like to do now is I'd
12 like to just -- I'm sorry.

13 DR. LIPICKY: Can I respond to Dan's question
14 about what the questions are about?

15 DR. DiMARCO: Surely.

16 DR. LIPICKY: I think I'll lead you through the
17 heuristic that's in the questions. It starts out posing
18 that one usually likes to think of having two trials that
19 meet their primary endpoints and that the p value from that
20 is .05 squared. That's the degree of certainty that one
21 would like to have that this is generalizable, it will
22 happen in the patient population, so on and so forth.

23 So, the questions start out saying can you come
24 to that conclusion from primary endpoints. If you can,

1 then that becomes the indication. If from the primary
2 endpoints one can say mortality and hospitalizations
3 decrease on carvedilol, that is an indication.

4 Well, one might not be able to or one might be
5 able to. If you can't, then you can look at the secondary
6 endpoints, create a similar circumstance where you are
7 convinced that secondary endpoints have been affected to
8 the degree that you would like to have for approvability,
9 then you have an indication.

10 Now, then you might say, well, you might not be
11 able to do that. So, then you can take retrospective
12 endpoints. Every time you take this step, there's clearly
13 an inference problem, and there are clear judgment
14 problems, and there are clear penalties you pay. And you
15 are asked to define them. So, you may be able to look at
16 retrospectively defined endpoints and say, I know what this
17 drug does. That is the indication.

18 Then you are given the opportunity in the very
19 last question of saying, I can't make up my mind like that
20 but it's got to be good for something.

21 (Laughter.)

22 DR. LIPICKY: And you get to vote on that.

23 DR. DiMARCO: Is that a suggestion we should
24 move on to the questions, Ray?

1 Are there any other members of the panel who
2 would like to ask questions directly of the sponsor? Marv?

3 DR. KONSTAM: There was one other question I
4 wanted to direct to Dr. Stockbridge. I still wasn't quite
5 clear what you were saying about protocol 240. You did a
6 different set of analyses than the sponsor did. Was your
7 conclusion was not still that it reached this primary
8 endpoint regardless of how you did the analysis?

9 DR. STOCKBRIDGE: The analysis that we did had
10 a p value for study 240 of less than .05. Is that the
11 question you asked me?

12 DR. KONSTAM: Yes, I guess so. So, it met its
13 primary endpoint any way you looked at it.

14 DR. STOCKBRIDGE: Well, again, what we looked
15 at was not exactly the same as what the protocol-specified
16 endpoint was. What we looked at included all-cause
17 hospitalization. It included rather than cardiovascular
18 hospitalization. It included all-cause death not cause-
19 specific death. So, in that sense, what we analyzed was
20 not the primary endpoint.

21 DR. KONSTAM: Now I'm more confused. If it was
22 looked at from the perspective of the primary endpoint, it
23 also reached it. Is that not right? That's correct.

24 DR. COLUCCI: Bill Colucci again.

1 It should be perfectly clear, if it isn't
2 already, the primary prespecified endpoints which were
3 quite cause-specific were strongly positive.

4 DR. KONSTAM: Right.

5 DR. COLUCCI: More conservative analyses done
6 by the FDA were also significant. And reduction of the
7 components of one, two -- leaving any single component --
8 all of those were also positive whether by cause-specific
9 or cause-nonspecific analysis. So, I've seen no analysis
10 of that study of any kind that was ever not statistically
11 significant.

12 DR. STOCKBRIDGE: If you leave out the
13 medications component from either the sponsor's analysis or
14 the FDA analysis which has no cause-specific component to
15 it, the p value goes up by a factor of 10 in both those
16 cases.

17 DR. KONSTAM: Right.

18 DR. KONSTAM: But it's still .05.

19 DR. STOCKBRIDGE: Well, the FDA analysis
20 started with a p value of .04 and went to .4.

21 DR. MOYE: Right, but leaving out the
22 medications is not per protocol.

23 DR. STOCKBRIDGE: That's true.

24 DR. MOYE: The per protocol included the

1 medications.

2 DR. STOCKBRIDGE: You're absolutely right.

3 DR. KONSTAM: Any interpretation of the primary
4 endpoint was reached. There's no debate it reaching its
5 primary endpoint. I just want to understand.

6 DR. MOYE: Now, the strength comes from the
7 medications presumably, but the endpoint prespecified
8 included the meds.

9 DR. KONSTAM: The strength comes from the
10 medications by Dr. Stockbridge's analysis but --

11 DR. LIPICKY: No. By anybody's.

12 DR. KONSTAM: I said it wrong. It falls away
13 from significant value if the analysis is done according to
14 Dr. Stockbridge's analysis which was not the per protocol
15 analysis. So, if you go per protocol and you take away the
16 medications, it's still sticks to --

17 DR. D'AGOSTINO: But, you know, we've been
18 making a big discussion about ignoring the primary outcome.
19 This is one case where the primary outcome did in fact turn
20 out to produce significance. We probably don't want to
21 wander too much away from that.

22 (Laughter.)

23 DR. DiMARCO: Any other comments from the
24 panel?

1 (No response.)

2 DR. DiMARCO: Let's get started with the
3 questions then. Question 1.1 is, study 240 had a primary
4 endpoint of time to the first event of sudden death, death
5 from progression of heart failure, hospitalization for
6 worsening heart failure, or sustained increase in a
7 specified group of heart failure drugs. Elimination of the
8 medications component of the endpoint from either the
9 sponsor's analysis, which included cause-specific mortality
10 and hospitalization, or the reviewers' analysis, which
11 included all-cause mortality and hospitalization, greatly
12 increases the p value from 0.003 to 0.029 and from 0.04 to
13 0.378, respectively, suggesting that most of the
14 statistical power lies in the medications component.

15 What effect does this observation have on the
16 clinical interpretation of the results of study 240?

17 Rob, do you want to start off?

18 DR. CALIFF: Well, I think this gets deep into
19 the heart of the philosophy of determining health effects
20 of a treatment. It's one thing to say that the drug has a
21 mechanism of action that improves a component of a person's
22 health. It's another to say that you improve the overall
23 health state of the individual or of the population. I
24 think it's not nearly as strong when you have a change in

1 the p value that's so substantial when you move away from
2 the cause-specific events. I think it's a point of
3 weakness that's fairly substantial.

4 DR. DiMARCO: Ralph, would you like to comment?

5 DR. D'AGOSTINO: I always like to make clinical
6 statements.

7 I just think that the study 240 -- somehow or
8 other, we have to take it on its grounds. It had a
9 protocol. It had a primary event. I think it is driven by
10 the medication component. It weakens the sort of
11 statistical power and so forth, but nonetheless it still,
12 on their groups, maintains the significance. So, I think
13 if we play statistical significance, I think we still have
14 a result here. It certainly does weaken it clinically,
15 though.

16 DR. DiMARCO: Jeff, I'll ask you.

17 DR. BORER: Yes, I agree with that. Certainly
18 eliminating the medications component weakens the strength
19 of the conclusions and the degree of consistency of the
20 data, but nonetheless, the study, as it was set out to be
21 done, achieved the goal that it set out to achieve. It
22 proved the hypothesis it tried to test.

23 In addition, from what I've read here and from
24 what I've heard, every other kind of analysis that could be

1 done of these data still comes up with a statistically
2 significant result in favor of the drug. Now, of course,
3 not all that overwhelmingly strong, but still statistically
4 significant. I'd like to see some confirmation from a
5 second trial, but I would accept this as a positive trial.

6 DR. DiMARCO: Would anyone else like to comment
7 on this question?

8 DR. CALIFF: Just one more little emphasis.
9 The big change is not taking away the drug effect or the
10 effect of counting the change in medication. The big
11 change is going from cause-specific to all-cause. Is it
12 right that we should be looking for overall health effects
13 that cause specific outcomes? Do you really care if you
14 die from heart failure or from something else?

15 DR. BORER: No. I agree with you about looking
16 at all-cause. I'm sorry. That's quite right. But even if
17 you do that, still the overall analysis of all-cause
18 hospitalization and all-cause mortality together is, as I
19 understand it, statistically significant.

20 DR. CALIFF: No. I think it's .378.

21 DR. DiMARCO: That's the one that goes to .378.

22 DR. CALIFF: I think it's a great cause-
23 specific answer to a question about how the drug works, but
24 as far as the overall health effect -- that's why I say it

1 concerns me that the p value goes all the way to .38 when
2 you count all-cause. If it just changed a little bit, I'd
3 be more comfortable.

4 DR. DiMARCO: Dr. Temple?

5 DR. TEMPLE: Can someone remind me? If you do
6 all-cause mortality plus all-cause hospitalization plus the
7 medications, what's the result of that? Because that's
8 what we are really talking about here. It's the morbidity
9 plus mortality endpoint that changes if you go to all-
10 cause, but what happens if you keep the endpoint as planned
11 but modify it in that way? Does anybody know?

12 DR. PACKER: Bob, that analysis hasn't been
13 done, but based on the magnitude of the effect on all-cause
14 mortality and all hospitalization, plus the medications --
15 and remember, it's a 2 to 1 randomization at 50 percent
16 lower risk. I have to emphasize this hasn't been done, but
17 you're combining two components which go very strongly in
18 the same direction. It's very likely that that will be
19 statistically significant even when the original primary
20 endpoint of 240 is broadened in a non-cause-specific
21 fashion. Of course, now that the committee has asked for
22 that analysis, it can be done.

23 DR. TEMPLE: Given that the results are largely
24 driven by the medication, it seems likely that it's going

1 to come out that way.

2 DR. STOCKBRIDGE: If I understood your question
3 correctly, that is the analysis that the FDA reviewers did.
4 It was non-cause-specific plus the medications. That gave
5 you a p value of .04.

6 DR. TEMPLE: Okay, but that was on a very much
7 reduced data set because you didn't find most of the
8 medication data adequate.

9 DR. STOCKBRIDGE: All of that is certainly
10 true.

11 DR. TEMPLE: I was just trying to distinguish
12 between two points that are being made. One, as Ralph
13 said, for better or worse, you live with roughly the
14 endpoints that they chose because we're not supposed to go
15 flipping away from endpoints any more than they are. And
16 if you do that and stick with the medication, it really
17 turns out not to matter very much whether you use cause-
18 specific or non-cause-specific because that's not the major
19 driver of that endpoint. So, it's not surprising.

20 It just means that what you've got here is an
21 endpoint that is mostly about worsening heart failure as
22 measured by medication use. It's not really a
23 mortality/morbidity, in some other sense, endpoint. It's a
24 more limited endpoint. You have to decide whether that's

1 clinically relevant or meaningful.

2 DR. KONSTAM: John?

3 DR. DiMARCO: Marv?

4 DR. KONSTAM: I think you could approach this
5 question from two different perspectives: a statistical
6 perspective and a clinical perspective.

7 From the statistical perspective, I think you
8 have to give this trial its due, as Dr. Temple was saying,
9 and as we go to beat up on other trials, as we'll come to,
10 that don't reach their primary endpoint, this one does and
11 we got to stick with that.

12 From the clinical perspective, Rob, I am
13 somewhat concerned, but I guess I'm not as concerned as you
14 sound to be about the change in the p values from the
15 medication difference when you take away the medications.
16 The p value rises in large part because the number of
17 events is falling, but in fact the other two contributors
18 are still going in the same direction for one point. And
19 for another point, it seems to me to be consistent with
20 other things in the data set. So, although it's obviously
21 a big driver to the magnitude of the p value and I'm a
22 little bit worried about it, I'm not that worried about it.

23 DR. CALIFF: But again, I'm responding less to
24 that than to the change from .04 to .378 which makes me

1 wonder if there's an excess of non-cardiac hospital
2 admissions in the carvedilol.

3 DR. COLUCCI: I think that Dr. Konstam's point
4 is very important. That study was empowered based on
5 estimates of the event rate for the three-component
6 endpoint so that it really is not empowered to see anything
7 when you take one of those away, particularly the one that
8 is the major contributor.

9 I think it is fair to go to a non-cause-
10 specific death and hospitalization, but really to take away
11 medications really just under-powers it tremendously. It
12 was prospectively designed to be empowered to this
13 endpoint.

14 The other thing to be said is that although
15 medications have traditionally not been quantified in big
16 clinical trials, they generally show up as an increase or a
17 decrease. This study had really the first and most
18 specific criteria for change in medications of any trial
19 that has been done so far. That required a 50 percent
20 increase that was sustained for over 30 days or the
21 addition of a new additional drug.

22 So, these are much more firm objective
23 endpoints for change in medication than have been used in
24 the past and I think are much less susceptible to the type

1 of criticism that is very justified because, after all,
2 diuretics are adjusted up and down, a little here and
3 there. But these are substantial changes that are
4 maintained for a substantial period of time.

5 DR. DiMARCO: Dr. Raehl?

6 DR. RAEHL: I think you just answered my
7 question, but to clarify, the change in medication to which
8 we're referring is primarily due to diuretic regimen
9 changes. Correct?

10 DR. COLUCCI: Or ACE inhibitors.

11 DR. RAEHL: There seems to be disagreement
12 among your --

13 DR. COLUCCI: The majority of changes were
14 diuretics. The majority were diuretics that were changed,
15 but it could have also been --

16 DR. RAEHL: Is that data anywhere in our review
17 that we could actually see how the medication profiles, if
18 you will, changed on an aggregate basis, that being a
19 primary driver?

20 DR. COLUCCI: I believe that's available.

21 DR. SHUSTERMAN: We don't have it here, but I
22 would agree with Dr. Colucci, probably diuretics are about
23 a half --

24 DR. DiMARCO: You have to use the microphone

1 please.

2 DR. SHUSTERMAN: It also included changes in
3 nitrates, changes in ACE inhibitors which made up the other
4 half. There were no changes in digoxin --

5 DR. RAEHL: So, the criteria was a 50 percent
6 increase in any of those medications, but about half of the
7 time it was about a 50 percent or more increase in
8 diuretics. Is that fair to say?

9 DR. SHUSTERMAN: Or the addition of a new
10 diuretic. Correct, yes.

11 DR. COLUCCI: It had to be at least a 50
12 percent increase in dose or a 50 percent increase in dose
13 of an ACE inhibitor or nitrate or other vasodilator. About
14 half of the time, that was the diuretic. The rest of the
15 drugs contributed to the other half.

16 DR. DiMARCO: Are there any comments with
17 regard to question 1.1?

18 (No response.)

19 DR. DiMARCO: Let's move on to number 1.2. We
20 are now moving to study 223. What clinical benefit was the
21 primary endpoint in the short-term phase? Rob?

22 DR. CALIFF: My reading of the short-term phase
23 is we didn't have any evidence of substantial clinical
24 benefit. We had ejection fraction and ventricular diameter

1 measurements that were improved. The primary clinical
2 endpoint was not affected. Those are nice and very
3 stimulating endpoints, but not measuring clinical status.

4 DR. DiMARCO: So, you would conclude that there
5 was no real demonstrated clinical benefit in the short-term
6 phase.

7 DR. CALIFF: If our goal is to understand
8 overall health benefits to the patients or populations,
9 there were none demonstrated.

10 DR. DiMARCO: Ralph, any comments?

11 DR. D'AGOSTINO: I agree with that.

12 DR. DiMARCO: Anyone on the committee have a
13 different opinion?

14 DR. GRINES: I don't remember that that data
15 was shown to us other than symptomatic data, just some of
16 the negative exercise data. But wasn't there a change in
17 ejection fraction? And we saw no symptomatic data. So, to
18 determine clinical benefit short-term would be very
19 difficult.

20 DR. CALIFF: All right, but the primary
21 endpoint of clinical benefit was the exercise endpoint.
22 Ejection fraction was definitely improved, but that's not a
23 patient-oriented endpoint.

24 DR. DiMARCO: So, I think that we can move on

1 to 1.2.2. Here the question is, what clinical benefit was
2 the primary endpoint in the long-term phase?

3 DR. CALIFF: I think we reviewed that ad
4 nauseam here. The wording is not specific. The analyses
5 have been done in a variety of ways, and probably by the
6 way we have come to as preferred way in this group, it's
7 marginal at .04 but it's there.

8 DR. D'AGOSTINO: I think that the protocol is
9 quite deficient in flagging what the long-term is going to
10 be about, and I don't see any way out of that. If you do
11 say that, well, give them the benefit of the doubt that
12 this hospitalization and death that you're involved with
13 there and you get a significance of .04 or .035 -- I forget
14 exactly what it was -- there's still the presence of these
15 other outcomes down the way, but I don't see how you can
16 just disjoint this particular analysis from the fact that
17 there were three other analyses going on.

18 DR. DiMARCO: Other comments from the committee
19 on that question?

20 DR. MOYE: I just need to be sure. Study 223
21 was the Australian-New Zealand study. Right?

22 Hopefully we want to call it a primary
23 endpoint, but the long-term phase, in any event, looked at
24 combined morbidity and mortality. Is that right? Isn't

1 that right?

2 DR. D'AGOSTINO: Yes.

3 DR. MOYE: And the p value for that was
4 provided as?

5 DR. CALIFF: .045.

6 DR. MOYE: Even though this was a prospectively
7 designed follow-up trial, there was no prospective
8 statement about what to do with these multiple
9 goals/objectives.

10 DR. D'AGOSTINO: It isn't even clear what they
11 were going to do with the particular variable. I do not
12 read it that they were necessarily going to analyze it.
13 I'm not clear why it was being collected, but certainly it
14 doesn't go on to your question.

15 DR. MOYE: The result becomes even more
16 skeptical.

17 DR. DiMARCO: Following up on that, is there a
18 possibility that baseline prognostic factors could to be
19 used to adjust in this study?

20 DR. WEBER: If I could ask a question. When
21 they are in fact used to adjust -- this is on slide 43 of
22 the handout we've got -- the p value seems to get quite a
23 bit stronger, especially when you adjust for New York Heart
24 Association class and ejection fraction and so forth. Is

1 there some explanation for why that is?

2 DR. CALIFF: I might comment on that since
3 we're doing that a lot prospectively now. It's sort of
4 hard to understand why you would adjust in a randomized
5 trial in the first place, but if you did it -- and I think
6 Lloyd Fisher commented on this before -- in general your p
7 value gets smaller because you're taking away some variance
8 in the estimates. That's about as far as my knowledge
9 goes.

10 DR. D'AGOSTINO: Or the other response to that
11 is that you only see it when the p value gets smaller. Why
12 would a sponsor present it if the p value is getting
13 bigger? So, it's not clear that it will always get
14 smaller.

15 DR. PACKER: Ralph? John, with your
16 permission. The sponsor did not propose doing any
17 covariate analysis here. It was done only in response to
18 an FDA request.

19 DR. D'AGOSTINO: I understand that. It was
20 just a comment. I was obviously being facetious.

21 But I think the .045 is what the result that
22 they wanted to produce is and we have to grapple with the
23 question of whether or not we think it should be adjusted
24 for multiple testing.

1 DR. DiMARCO: Any other comments? Dr. Temple?

2 DR. TEMPLE: What's your answer to your own
3 question? What sort of adjustment might there be? Well,
4 there were three endpoints.

5 DR. D'AGOSTINO: There were three endpoints.
6 No, I think --

7 DR. TEMPLE: One of which made it.

8 DR. D'AGOSTINO: One of which made it. I think
9 it's a good question and I don't really know the answer
10 because I'm not completely convinced that one has to link
11 the first with the second. I think you might be able to
12 argue -- and I was actually hoping that there would be a
13 discussion -- that in fact you can separate the front piece
14 from the back piece and buy power or buy alpha of .05 for
15 both pieces. I think that's a reasonable suggestion to
16 make here. So, I guess I have an opinion, but I'd really
17 like to see how other people sort out that.

18 DR. TEMPLE: That seems important because the
19 thinking about this study goes in two stages. One is can
20 you decide that the second phase was designed to study
21 anything in particular. Once you get over that hump, then
22 you have to figure out what to do with the nominal p value
23 they observed. So, I guess I hope there's some discussion
24 too.

1 DR. DiMARCO: Dr. Borer?

2 DR. BORER: Personally I'm relatively
3 unconcerned about dissociating short-term from long-term.
4 I don't think that's intrinsically unreasonable if that's
5 what you said you were going to do. It seems as if they're
6 fairly potentially self-contained analyses that have
7 nothing to do with one another.

8 But hump number 1 here is the one that I'm
9 having a little trouble with. I accept the explanation
10 that Milton and the others gave about the intention of the
11 investigators, but I'd feel a lot better about that if it
12 were clearly stated somewhere where I could understand it
13 better. So, that's the trouble that I'm having with this.

14 If it was actually a prespecified hypothesis to
15 be tested, that the combined endpoint would improve on the
16 drug at 18 to 24 months, I would accept the p value as
17 being important and I would say 223 corroborated 240 and
18 I'd be very happy. But I'm not sure of the intent of the
19 sponsor and the investigators in doing the study.

20 DR. PACKER: Jeff, the correspondence that
21 documents this can be shared with the committee. I think
22 everyone recognizes that 223, perhaps because it was an
23 investigator-initiated protocol, could have and should have
24 been better written and more clear.

1 But the written materials that the
2 investigators have provided make it clear what their intent
3 was, make it clear the division separated from between the
4 short and long-term phase, and that they defined mortality
5 and major morbidity a priori as all-cause hospitalization
6 and all-cause mortality, the least biased of all the
7 analyses.

8 DR. D'AGOSTINO: I think that it really comes
9 down to, in terms of our opinion as giving advice, it's not
10 in the protocol. Would we as experts in statistics and
11 clinicians be willing to separate the two and would we be
12 willing to let the second phase live with its .045? I
13 don't think there's any hope of getting something out of
14 your correspondence.

15 DR. PACKER: If I could add, I think everyone
16 appreciates the uncertainty in the original protocol, and I
17 think that was part of the motivation why the FDA asked for
18 the analyses of 220 and 221. The concept was that if one
19 could find confirmation of exactly the same analysis,
20 combined morbidity/mortality, not cause-specific in other
21 trials in the U.S. program -- and all the trials that could
22 find it were looked at. And it was found. It was
23 retrospective. The individual component, the morbidity
24 component, was prospective. The combined was

1 retrospective. If one could see it there and one sees it
2 there with small p values, one can get additional comfort
3 about the effects seen in 223.

4 DR. KONSTAM: John?

5 DR. DiMARCO: Marv?

6 DR. KONSTAM: I haven't heard any viewpoint on
7 the panel that this trial has any hope of standing on its
8 own. The question then is, what support, if any, does it
9 give to 240? That's obviously the question.

10 DR. D'AGOSTINO: Can I interrupt? I'm sorry.
11 I think it has to stand on its own to answer the question.
12 We are being asked does it stand on its own. Am I wrong on
13 that?

14 DR. TEMPLE: Not solo, but in combination with
15 the others.

16 DR. D'AGOSTINO: No, no, but I mean the
17 question that we have before us. Do we have the
18 traditional two studies?

19 DR. DiMARCO: Two studies, yes. This has to be
20 one study that's accepted.

21 DR. KONSTAM: Well, let me just finish my
22 comment. I think the issue to me is do I believe this
23 endpoint. Can I look at the whole data set and believe any
24 endpoint? That's what I'm grappling with. We have a study

1 that's positive and that's 240. In my view I agree with
2 you. The study clearly doesn't stand on its own.

3 So, the issue then becomes is there any value
4 in it at all to me. I guess I have to say there is some to
5 me.

6 By the way, why doesn't it stand on its own? I
7 think all of us agree that we don't see a primary endpoint.
8 So, there's a big problem there.

9 DR. LIPICKY: But, Marvin, you'll be able to
10 say something about that when you get down the end of the
11 list.

12 DR. KONSTAM: Oh, is that right?

13 DR. LIPICKY: Yes, because you'll be able to
14 say I couldn't draw a conclusion in number 1. You might be
15 able to use it in number 2. Well, if you can't draw a
16 conclusion in number 2, you might be able to use it in
17 number 3. Well, if you can't draw a conclusion in number
18 3, number 4 says can you draw any conclusions at all.

19 DR. KONSTAM: Well, let me ask you. The issue
20 to me is, is there a primary endpoint that is met?

21 DR. LIPICKY: Right.

22 DR. KONSTAM: And if there is a primary
23 endpoint that is met, it's in protocol 240.

24 DR. LIPICKY: Correct.

1 DR. KONSTAM: Then the question for me is, is
2 there any corroboration for that anywhere in the data set?

3 DR. LIPICKY: You were asked on some primary
4 endpoint here, 223, and the answer is yes or no.

5 DR. KONSTAM: Is it not possible to draw some
6 corroboration regarding a primary endpoint in study A from
7 another study that does not meet its primary endpoint? Is
8 that not possible? That's what I'm asking.

9 DR. LIPICKY: We're talking about making a
10 decision here about whether we have two studies that have
11 met a primary endpoint. Okay? So, that is the question
12 under consideration.

13 Later you'll be able to say, well, maybe not
14 but something happened here. You will get the opportunity
15 to answer the thing you want to address. You need to hear,
16 can you make it clean? And either you can or can't.

17 DR. PACKER: Ray, I just have a question again,
18 with John's permission. If I understand it, the pivotal
19 question for this part, which is 1.3, is prefaced by the
20 phrase "with appropriate consideration of the supporting
21 evidence from primary and secondary endpoints of these and
22 other clinical trials," which I think addresses Marv's
23 issue directly.

24 DR. LIPICKY: Well, he has to make a decision

1 as to whether 223 satisfies the condition for saying that
2 it met a primary endpoint. If he wants to draw on other
3 trials, as you want him to, he can do that.

4 DR. PACKER: That's what your question asks him
5 to do.

6 DR. WEBER: It asks for secondary endpoints
7 too.

8 DR. CALIFF: I think we need to answer the
9 technical question of whether we're accepting that there is
10 a primary endpoint in 223 which is less than .05.

11 DR. DiMARCO: That we're going to accept.

12 DR. CALIFF: Right. Although I'm an advocate
13 of efficient trial design and trying to answer as many
14 questions as you can, it's hard to accept totally unhinging
15 within the same trial these four endpoints. It's kind of
16 like taking four shots off the tee and saying, I'll take my
17 best and not worry about the other three.

18 I don't think it ought to be a severe penalty
19 because there are clearly sort of two things being
20 addressed here. But I think this is where even I would ask
21 for a statistician's --

22 DR. D'AGOSTINO: I could have given my opinion
23 immediately, but I thought that might be inappropriate.

24 I would say, no, this doesn't make it. I think

1 that my sense that this doesn't make it on its own because
2 of the questions with the four possible outcomes and so
3 forth. But we do pick up an alternative way of bringing
4 this back to us with the next question. So, to be clean, I
5 think this is a no. We can't ignore those other pieces.

6 DR. DiMARCO: I think we've gotten to the point
7 then that we can probably take a vote on 1.3 which is
8 really the question we're dealing with. Are we going to
9 accept both of these as trials which stand alone
10 essentially?

11 DR. D'AGOSTINO: Well, 1.3 says, "other
12 clinical trials."

13 DR. DiMARCO: That's right.

14 And the question is, should carvedilol be
15 approved for the treatment of heart failure on the basis of
16 p less than 0.05 on the primary endpoints in each of two
17 adequate and well-controlled studies? And that refers to
18 240 and 223.

19 DR. TEMPLE: We need to clarify this. The
20 order of this is that first you look at individual studies
21 and their primary endpoints. Then you look at other
22 endpoints, secondary endpoints, and then you go for it and
23 look at anything you want to.

24 So, this is the one about primary endpoints.

1 The question here, just to be clear -- as I read it again,
2 it's not perfectly clear -- is, based primarily on two
3 studies that may have met fully, partly, whatever their
4 primary endpoints -- and you're allowed to think about all
5 the other stuff -- does this make it in the conventional
6 way, the conventional way being you have two well-
7 controlled studies that demonstrate something that they set
8 out to demonstrate. That's sort of the conventional way.

9 But we didn't want to say you couldn't even
10 think about all those other things, so that's why 1.3 says,
11 oh, well, you can think about those things. But the
12 primary focus here is on those two studies and what they
13 showed on their primary endpoints.

14 I don't know if that helps.

15 DR. DiMARCO: Is everybody clear on the
16 question now? Okay.

17 Ralph, do you want to start?

18 DR. D'AGOSTINO: Well, again, I just was thrown
19 an oddball there I guess because I'm still looking at the
20 statement that says "supporting evidence from primary and
21 secondary endpoints of these and other clinical trials." I
22 think that "other clinical trials" is very important.

23 These two studies standing on their own --
24 first, 240, we voted that it makes it. I think 223

1 standing solely on its own doesn't make it, but I think
2 223, in conjunction with these other analyses we've seen,
3 does make it. So, my answer is yes to this question. I
4 hope I'm reading it correctly.

5 DR. TEMPLE: Well, Ray may want to comment too,
6 but I think that's what we were asking you. As everyone
7 has said, there are things about 223 that are not perfect,
8 to say the least. On the other hand, it's not nothing, if
9 I hear you.

10 So, the question here is, well, along with that
11 which is flawed and has problems and the other study and
12 the other data -- now, you may want to spend some time
13 discussing the other data before you give a yes, but that
14 was the idea of this question.

15 Ray, do you buy all that?

16 DR. LIPICKY: Then the decision is not being
17 made on the basis of meeting the primary endpoints in two
18 trials. I must admit there's more emphasis to those words
19 than probably belong in that question, and I'd like to take
20 those words out.

21 DR. TEMPLE: The reference to the other stuff.

22 DR. LIPICKY: Because people get a chance in
23 later questions to say, oh, yes, the totality of evidence
24 is overwhelming. The question that number 1 is addressing

1 is can you get there from primary endpoints in two trials.

2 DR. D'AGOSTINO: I don't want to lose the way
3 this is worded. So, somebody keep it for a later
4 discussion. If we drop that reference to other trials and
5 other supporting data, I would say, no, we don't have two
6 clean trials.

7 DR. TEMPLE: Maybe that question is really part
8 of 2. I think that's what Ray is saying.

9 DR. LIPICKY: Yes. Those words don't belong in
10 1. It was an error to get them there.

11 DR. STOCKBRIDGE: Could I argue that the words
12 really ought to belong in 1 since I put them there?

13 (Laughter.)

14 DR. STOCKBRIDGE: I think what one normally has
15 is something better than two trials with a p of less than
16 .05. One normally has two trials with a p of less than .05
17 plus secondary endpoints that help you feel good, that make
18 you believe that the primary endpoint is a plausible one,
19 that the primary endpoint finding is a plausible one.
20 One's confidence is usually better than is expressed by two
21 trials and only one finding in each of those trials.

22 DR. D'AGOSTINO: I hope the FDA is going to pay
23 for my stay tonight because I can see I'm going to miss my
24 plane.

1 (Laughter.)

2 DR. D'AGOSTINO: The "other clinical trials" is
3 the piece. If you want to feel good about these trials and
4 so forth, there are things to feel good about. It's the
5 "other clinical trials" I think that is very important in
6 terms of the way I would vote.

7 DR. DiMARCO: So, the vote is?

8 DR. D'AGOSTINO: If we remove that phrase from
9 it, it's no, these trials don't stand on their own.

10 DR. DiMARCO: We've got some discrepant from
11 our two FDA representatives here. Does the committee want
12 to take that phrase out and just say the trials have to
13 stand on their own? Maybe I'll just take a hand vote. How
14 many want to leave it the trials have to stand on their own
15 at this point in this question?

16 DR. WEBER: Why don't we do it both ways very
17 quickly, John?

18 DR. DiMARCO: Okay.

19 DR. CALIFF: Yes. I think it's important to be
20 clear that if we're saying we're going to make an exception
21 to a clear-cut standard. So, the first question without
22 the phrase.

23 DR. DiMARCO: So, we'll vote on this both with
24 and without the phrase. The first time we'll vote without

1 the phrase, so that the trials have to stand absolutely on
2 their own as two independent trials with significant
3 results.

4 DR. D'AGOSTINO: No.

5 DR. BORER: I'm sufficiently concerned about
6 all the issues that have been raised about 223 that I would
7 reluctantly have to say no as well if we can only consider
8 those two trials.

9 DR. DiMARCO: Cindy?

10 DR. GRINES: I think 240 meets its endpoint.
11 It sounds like 223 probably does not, although it has
12 clinical benefit. So, I guess I would answer no to 1.3.

13 But I'd like to point out that the materials
14 that we were given state that in reconsidering carvedilol,
15 the committee is reminded that Federal regulations
16 pertaining to approval simply call for evidence of benefit
17 from clinical trials. They specifically say that the
18 regulations do not specify a p less than .05 on primary
19 endpoints in two studies. So, I think for our committee to
20 be clear on that.

21 DR. DiMARCO: Yes. I don't think this is going
22 to be the final word on whether the recommendation will be
23 for approval or not. This is just to answer this question.

24 Rob?

1 DR. CALIFF: No.

2 DR. DiMARCO: I'll vote yes.

3 DR. MOYE: I think that 240 is fine, but 223 in
4 my view is extremely problematic, so I say no.

5 DR. RAEHL: No, for the same reasons.

6 DR. WEBER: I also, I guess like everyone, have
7 a little bit of a problem with 223, and this is a little
8 bit of a phony vote because if you told me there was
9 absolutely no other data and everything had to rise and
10 fall on 240 and 223 and that was it, I'd vote yes. But
11 knowing that there's other stuff, I can have the luxury
12 of --

13 (Laughter.)

14 DR. WEBER: -- a throwaway vote, as Lem calls
15 it.

16 DR. RAEHL: That's why I jumped ahead.

17 DR. KONSTAM: I don't see a primary endpoint in
18 223, so I vote no.

19 DR. RODEN: No.

20 DR. DiMARCO: So, if we throw out the phrase
21 "with consideration of the other trials," the committee has
22 voted as we've heard.

23 What if we keep the phrase in?

24 DR. D'AGOSTINO: There's a grab bag of these

1 secondary endpoints, some of which are significant, some of
2 which aren't significant, and so forth, but there is a
3 direction to them. Then there are these other bits of
4 information that come from the other trials. Nothing is
5 without fault, but I think that my hearing of the
6 presentation and my reading of it is that they are very
7 consistent, and I would say with this other supporting
8 information, I would vote yes.

9 DR. DiMARCO: Jeff?

10 DR. BORER: Yes, I would echo that view. I
11 think with all the problems -- and I see a lot of problems
12 -- still the overall consistency through analysis after
13 analysis and analysis that was specified by the sponsor and
14 analyses that were asked for by the FDA, they all seemed to
15 go in the same direction. So, I would say the same thing
16 as Ralph did. I would say yes if we include everything.

17 DR. DiMARCO: Dr. Temple, do you have a
18 comment?

19 DR. TEMPLE: As you do this, could you identify
20 somewhat more specifically what's making you feel that way?
21 I ask that because in the later questions, we point out
22 that there were some specified secondary endpoints like
23 globals, the New York Heart, and all that. That's one
24 category of stuff. Then there's also the mortality plus

1 morbidity analyses, and that's a different category of
2 stuff. So, not to argue the point but say which of those
3 or both are convincing.

4 DR. D'AGOSTINO: I was trying to say both
5 actually in my answer. I think that the global, the New
6 York categories. To me I'm more persuaded by the mortality
7 and morbidity analyses, but I do think the secondary also
8 are important.

9 DR. BORER: Yes. That's exactly what I would
10 say. I think the consistency of the mortality and
11 morbidity data are most persuasive, but it's nice when you
12 see the matrix, seeing that for most of the other endpoints
13 that may not even be related in terms of pathophysiology to
14 the -- mortality and morbidity may not be related all that
15 closely, anyway -- that even there the results all
16 generally tend in the same positive direction with the
17 drug.

18 DR. DiMARCO: Cindy?

19 DR. GRINES: I'm going to answer yes to
20 question 1.3, and it's primarily based on the statistical
21 reviewer's table, table 9 on page 16, where it outlines a
22 lot of the different endpoints. It seems that the majority
23 of the studies showed either a trend or a significant
24 difference in favor of mortality. All showed ejection

1 fraction. Most showed improvements in New York Heart
2 Association class, subjective scores, objective scores,
3 progression of heart failure. And I think it's very
4 consistent throughout the trials.

5 DR. DiMARCO: Rob?

6 DR. CALIFF: I'll make a few comments here.
7 I'm going to say yes too, but it's kind of in the blind pig
8 finds an acorn category because the primary endpoints by
9 themselves don't cut it. We end up with this sort of
10 mishmash of, in all different kinds of studies, all
11 different kinds of endpoints being positive. You get the
12 feeling that something good is in there. It's not very
13 directed in the way that you'd like to see it.

14 First of all, I know we're going to get to
15 this, but it's good to see some actual patient assessment
16 and physician assessment in a blinded way. I think that's
17 very reassuring.

18 Then the last thing. The one contingency I
19 have is I am still hung up on the run-in phase. The
20 preliminary, sort of off-the-cuff data looks good, but I'd
21 like reassurance that since this was not primary,
22 secondary, or even tertiary in my mind in terms of the
23 global endpoint of death and all-cause hospitalization,
24 that if you did the worst case analysis, you would get

1 something like a p value of .01 or .001 in favor of
2 treatment. It looks like it's going to be that way, but if
3 you throw in everything bad you can, make it the worst
4 case, it still looks good. Even though it wasn't looked
5 for, I don't see how you can turn your back to that. I
6 think it's compelling.

7 DR. DiMARCO: So, that's a yes.

8 DR. CALIFF: Yes.

9 DR. DiMARCO: My vote was earlier yes, and I
10 would just say I'd continue to vote yes. I really think
11 that this part of the question is almost sort of like 1.8
12 instead of question 2 because what we're talking about is
13 we're accepting something less than the perfect study in
14 223 because of all the other evidence which has a broad
15 pattern of consistency. So, I sort of think we're edging
16 towards question 2, but again I'll vote yes.

17 DR. MOYE: I'm going to vote no. I think that
18 the evolution of clinical trial methodology should be for
19 more stringent requirements not less stringent, and I think
20 that the investigators and sponsor have the resources and
21 the intellectual horsepower to do things right. I don't
22 think they did things right in 223.

23 I think that the table that was mentioned,
24 table 9, is not persuasive because it comes before table 11

1 which shows a great many more study endpoints and p values
2 and shows positive ones as well as negative ones.

3 In the absence of prospective statements by the
4 sponsor as to how to be guided through this, I again have
5 the freedom to choose a very conservative track, and the
6 conservative track is concerned for the risk of a type 1
7 error in the population at large. I think looking at a
8 hodgepodge of secondary endpoints makes it very likely that
9 we are misleading the population at large.

10 I can't imagine writing a label that lists a
11 host of different benefits and then says, but we're
12 probably wrong on at least one of them, and that's
13 tantamount to what we're doing by looking at this
14 collection of secondary endpoints in a very unstructured
15 manner.

16 So, my vote is no.

17 DR. DiMARCO: Mike?

18 DR. WEBER: Well, I guess like most people I
19 have shared concerns about 223, and I think as much as
20 anything, it's an irritation that it took us so long to get
21 to the real story of 223. I don't think that prospectively
22 before the study began, the investigators had talked about
23 short-term and long-term endpoints. I think most of us now
24 have a pretty good sense of how the study evolved, and

1 there's nothing wrong with how the study evolved. We're
2 all investigators. We know how things happen and how new
3 ideas come along during the course of a study.

4 I think all of us around this table are
5 experienced enough to know that those data can still be
6 very helpful. They may not be perfect. They may not
7 satisfy Dr. Moye's strict rules for clinical trials, but it
8 would have been very helpful. And it's annoying that it
9 took us so long to get at it.

10 I in fact think the data from 223 are quite
11 useful. They may not be perfect, but they're quite useful.

12 I think the point that Cindy made was
13 important, that ultimately we don't have to be judges of
14 the perfection of trials. We have to be satisfied that a
15 drug is efficacious and beneficial, and I think obviously
16 most of us are.

17 I'm also reassured that some of the less
18 dramatic findings, the assessments by the physicians, the
19 assessments by the patients, which were done blinded of
20 course, went very strongly in the same direction as the
21 more objective findings.

22 So, I really have no difficulty in believing
23 that carvedilol is a good drug for the treatment of
24 congestive heart failure however it may ultimately be

1 labeled, and I vote yes.

2 DR. RAEHL: I'm influenced by the morbidity and
3 mortality data first but also by the overall trends of some
4 of the secondary factors as described in table 9, in
5 particular the Heart Association classification and
6 ejection fraction. So, therefore, I'll vote yes.

7 DR. KONSTAM: I'm going to vote yes. To me the
8 crux of the matter is this. We have one trial with a
9 positive primary endpoint and that's 240. I guess the only
10 way I can approach it then, without another primary
11 endpoint that's positive, is do I believe the results of
12 240, yes or no, and my answer is, yes, I do believe the
13 results of 240.

14 The reason I do comes from a variety of
15 different sources of information. The first is that 223
16 looks similar although it is not a primary endpoint, but I
17 think there's evidence in 223 that pushes me toward
18 believing 240.

19 I think there's evidence in 220 and 221 that
20 pushes me toward believing the results of 240, again
21 totally the result of post hoc analyses, and therefore no
22 way they could stand on their own, but again they push me
23 toward believing the results of 240.

24 What also pushes me toward believing the

1 results of 240 is that I think there is evidence in the
2 data set toward each of the individual components of 240,
3 again not from any one primary endpoint, but I can't help
4 being influenced by the overall direction and magnitude of
5 change of the overall mortality, which is a component of
6 240, and although obviously not a primary endpoint and it
7 wasn't a single trial to look at it, I can't help but
8 recall the overall magnitude of this non-specified
9 endpoint, nevertheless a very important endpoint,
10 mortality, over the whole data set, again using it to
11 support the fact that I believe the components of 240.

12 Finally, I would say that I think that the
13 results of 240 are believable from what else we know.
14 They're not like a Vesnarinone result, for example, that's
15 out of the blue and nobody would have expected based on
16 what we know about that drug or other inotropic drugs.
17 It's in the setting of sort of 20 years of thinking about
18 beta-blockers and a lot of trends in similar directions
19 that one can find in the literature about beta-blockers.
20 So, I guess I don't find the results of 240 a surprise.

21 So, for all of those reasons, I believe the
22 result of 240 and therefore I vote yes.

23 DR. DiMARCO: Dan?

24 DR. RODEN: As I read this question, we're

1 being asked, whether on the basis of these and other
2 clinical trials, carvedilol should be approved for the
3 treatment of heart failure, blah, blah, blah, having
4 reached primary endpoints in two adequate and well-
5 controlled studies.

6 Now, I agree with everything that Marvin says,
7 including the Vesnarinone comment and the decades of
8 experience with beta-blockers, but I for exactly that
9 reason vote no. There aren't two adequate and well-
10 controlled trials.

11 DR. LIPICKY: So, has anyone kept track of the
12 vote?

13 DR. DiMARCO: Yes. The vote is 8 to 2.

14 DR. LIPICKY: 8 to 2.

15 DR. DiMARCO: Yes.

16 DR. LIPICKY: So, if it's 8 to 2 to approve,
17 then we are done.

18 DR. DiMARCO: Yes, because the next three
19 questions all start "if not."

20 DR. LIPICKY: Correct.

21 But before we quit, I'd like to find out two
22 things so I understand the sense of the committee.

23 So, what does carvedilol do?

24 (Laughter.)

1 DR. LIPICKY: Can someone tell me? Should it
2 be allowed to claim that it saves lives?

3 DR. KONSTAM: We haven't discussed that.

4 DR. LIPICKY: Should it be allowed to claim
5 that it decreases the progression of heart failure?
6 Because that's what hospitalizations and so on were in the
7 past, but this is all-cause hospitalization you guys
8 settled on.

9 Should it be allowed to claim it makes people
10 feel better?

11 And by not going through all the rest of the
12 questions, we weren't ever able to get that commitment.
13 Would somebody -- anybody -- tell me what they think
14 carvedilol does?

15 DR. WEBER: Could I ask the sponsor? You
16 started out today by saying you were not seeking a
17 mortality claim. Is there something you know that we don't
18 know?

19 (Laughter.)

20 DR. LIPICKY: Yes. It doesn't make it.

21 DR. WEBER: I'm getting back to the questions
22 Dr. Lipicky has just asked.

23 DR. LIPICKY: You should not ask the sponsor
24 anything now. You as a committee have said approve it. I

1 want to know for what.

2 DR. KONSTAM: Ray, based on the --

3 DR. LIPICKY: Okay? Tell me. Don't base
4 anything. Just say the words.

5 DR. KONSTAM: I want to look up the primary
6 endpoint of 240 before I answer the question.

7 (Laughter.)

8 DR. LIPICKY: Progression of heart failure, a
9 combined endpoint.

10 DR. KONSTAM: Does it say that in the protocol?

11 DR. LIPICKY: Yes.

12 DR. KONSTAM: Okay, then that's what I would go
13 with.

14 DR. LIPICKY: Yes. It was combined endpoint
15 progression of heart failure.

16 DR. RODEN: I actually think symptom relief of
17 heart failure. I think hospitalization is a very tough
18 endpoint to figure out what it means especially with a drug
19 that can be unblinded so easily.

20 So, I think the data, as I see them, say that
21 carvedilol doesn't do anything bad. There's this decades
22 of experience that Marvin has pointed out, and most of the
23 studies say that there is some relief in some of those
24 indices of function, some improvement in some of those

1 indices of function. Whether that's progression of
2 disease, which I think is a pretty broad kind of claim, or
3 relief of symptoms, which I think is a more constricted
4 claim, I'll let Ray decide.

5 DR. PACKER: Dan, don't you think
6 hospitalization is harder than symptoms? Firmer. I don't
7 mean harder -- actually harder to achieve, yes.

8 DR. RODEN: No, and I think that
9 hospitalization patterns in New Zealand may be very
10 different from hospitalization patterns in Los Angeles
11 compared to Des Moines, Iowa.

12 DR. PACKER: But you're seeing it
13 geographically all over the world.

14 DR. RODEN: Well, I think the physician
15 practices are different and I think clinicians approach
16 patients with tachycardia differently from patients with no
17 tachycardia and heart failure. So, I think that that's
18 actually less firm.

19 DR. PACKER: I need to say that because
20 hospitalization is in vogue now as a heart failure
21 endpoint.

22 DR. RODEN: I guess except in California where
23 no one goes into the hospital.

24 DR. CALIFF: Let me speak out in favor of

1 hospitalization as an endpoint. I think although there are
2 clearly different rates of hospitalization in different
3 societies and health care systems, the relative difference,
4 if shown to be constant is very important and represents
5 clearly something that's bad for the patient, which is what
6 we're charged to deal with.

7 DR. KONSTAM: What I would vote for is indices
8 of morbidity. It reduces the frequency of indices of
9 morbidity.

10 DR. LIPICKY: The indication would be this is
11 for decreasing the incidences of morbidity.

12 DR. KONSTAM: Of indicators of morbidity.

13 DR. LIPICKY: Indicators of morbidity in
14 patients with congestive heart failure.

15 DR. KONSTAM: That's a first cut, yes.

16 (Laughter.)

17 DR. LIPICKY: Can anyone do better than that?

18 DR. DiMARCO: I would go actually what the
19 endpoints in the trial were which are complications of
20 congestive heart failure --

21 DR. LIPICKY: But what were they?

22 DR. DiMARCO: -- which include death,
23 hospitalization, and --

24 DR. LIPICKY: So, they get a mortality claim.

1 DR. CALIFF: No, it's not a mortality claim.
2 It's a composite claim that includes mortality.

3 DR. LIPICKY: Death is in there, though.

4 DR. DiMARCO: Death is in there because that's
5 what we voted.

6 DR. KONSTAM: It's a little confusing if you
7 say it that way, though, because it sounds like we're
8 saying there's an effect on mortality. I would say that
9 mortality is an indicator of morbidity.

10 (Laughter.)

11 DR. WEBER: You'll get no argument from anyone
12 on that.

13 But a number of the trials used the combined
14 morbidity and mortality endpoint, and it was significant.
15 How are you going to separate them out?

16 DR. LIPICKY: All right, I understand. So,
17 that clarified it a little bit, well enough so that we'll
18 be able to argue.

19 Then I'd like the committee to argue with me
20 when I assert that. What you all said was if you don't
21 make it with your primary endpoints, root around in your
22 data and find retrospective endpoints that sound good and
23 you can wow us.

24 DR. KONSTAM: No.

1 DR. LIPICKY: No.

2 DR. KONSTAM: Not at all.

3 DR. LIPICKY: Well, how did you make that
4 decision?

5 DR. KONSTAM: Well, I already told you. The
6 issue is that we have a primary endpoint that's positive,
7 and getting back to the discussion --

8 DR. LIPICKY: One trial.

9 DR. KONSTAM: Right, exactly.

10 And getting back to the discussion from this
11 morning, I guess the only thing I'd feel comfortable
12 commenting on is whether or not I believe it based on the
13 entire --

14 DR. LIPICKY: One trial?

15 DR. KONSTAM: That's right. Do I believe that
16 that finding in that trial is positive or not? I do feel
17 that I believe the result of that trial based on many other
18 things in the data set.

19 DR. LIPICKY: So, you believe the results of
20 study 240 based on seven other trials.

21 DR. KONSTAM: I could go through it again.

22 DR. LIPICKY: Well, that's what there are,
23 seven other trials.

24 DR. KONSTAM: Specific elements of those

1 trials.

2 DR. LIPICKY: But your conclusion that those
3 other trials support 240 is because there were some p
4 values for totally retrospectively defined endpoints.

5 DR. TEMPLE: Ray, that's incorrect and you
6 mustn't keep saying that. Most of those endpoints were
7 prospective. They were just secondary.

8 DR. LIPICKY: Which ones?

9 DR. TEMPLE: Which ones were secondary? Death,
10 global --

11 DR. LIPICKY: This is mortality and all-cause
12 hospitalization. You invented that endpoint yourself.

13 (Laughter.)

14 DR. TEMPLE: Yes.

15 DR. LIPICKY: Okay. There's no question that
16 it's retrospective.

17 DR. TEMPLE: Ray, if you want them to use their
18 official secondary endpoint which is cause-specific, they
19 win on that too.

20 DR. LIPICKY: That was not a secondary endpoint
21 in any protocol. It was also a made-up endpoint.

22 DR. TEMPLE: This committee told us several
23 things and it's perfectly clear to me what they told us.
24 They said they do not agree that just because you fail on

1 your primary endpoint, you can never learn anything from
2 your secondary endpoints.

3 DR. LIPICKY: I --

4 DR. TEMPLE: I'd like to finish.

5 DR. LIPICKY: But --

6 DR. TEMPLE: I want to finish. Thank you.

7 (Laughter.)

8 DR. TEMPLE: They told us that. They were very
9 clear on it.

10 They also said that there were certain kinds of
11 other endpoints, like the combination of all-cause
12 mortality and morbidity, that are so persuasive in this
13 setting that they're even willing to believe that. Now,
14 that's debatable. Everybody can argue about that.

15 DR. LIPICKY: That's fine.

16 DR. TEMPLE: But that's what they told us.

17 DR. LIPICKY: I just want to be sure that I
18 understood them that retrospective endpoints that never
19 were stated anywhere at all are perfectly okay.

20 DR. KONSTAM: As an element of corroboration.

21 DR. LIPICKY: No, this isn't corroboration.
22 This replaces a trial. You have a trial and you're trying
23 to make up a second. Is that not what corroboration is?
24 How do you verify?

1 DR. KONSTAM: No. Again, the only question I
2 keep asking myself is do I believe the result of that one
3 trial that is clearly positive.

4 DR. LIPICKY: And you do that by?

5 DR. KONSTAM: Well, I'm using the word
6 "corroboration." The question is, do you need another
7 positive primary endpoint in order to say that? And I'm
8 saying no. I believe that without another primary
9 endpoint.

10 DR. LIPICKY: Fine, but you said that more than
11 that, that you could make up the endpoint. We need to be
12 certain that we understand exactly what you think.

13 DR. KONSTAM: Yes. I think in some cases --

14 DR. CALIFF: Ray, it sounds to me like there
15 are a variety of different reasons why people were swayed.
16 In my case it actually was -- I think you're close to being
17 right, but it's just that the endpoint that, as you say,
18 was "made up" is the big one. It's something that's, at
19 least in my mind, impossible to ignore if it's
20 overwhelming, even if you weren't looking for it, even if
21 you didn't think you were going to find it.

22 And it's there in study after study. You put
23 them all together. It's still there. If you count in the
24 deaths in the run-in phase, it's still there.

1 DR. LIPICKY: We would have gotten into all of
2 this if you hadn't answered the first question yes. How do
3 you know it's there? Because what you've done --
4 understand what you have done.

5 For primary endpoints it's pretty clear what
6 you're doing. Two .05's is .025 squared.

7 Now you get into the secondary endpoint
8 business because the primary endpoints don't get you to the
9 level of confidence you want. What are the p values you
10 need for the secondary endpoints? At least they were
11 mentioned. Certainly you're not talking .05 anymore.
12 You're elevating these guys to some status that is
13 different from what a secondary endpoint is. You're out of
14 this .05 stuff, and I would have liked to have seen what
15 you thought was significant and at what level you thought
16 it was significant.

17 Now even if it's a big-deal, retrospective
18 endpoint, you're really elevating that guy to something
19 enormous, of enormous status. It is the same as a primary
20 endpoint for purposes of approvability.

21 What p value tells you that it's there study
22 after study?

23 DR. CALIFF: Actually I think this is a very
24 important point. We might be sharper on it tomorrow, but

1 certainly in monitoring clinical trials -- and I think
2 somebody may have said this in one of the briefing
3 documents -- when you hit a p value of .001 for all-cause
4 mortality, for example, that's kind of my choking point to
5 say it's kind of hard to ignore this and you may be
6 crossing the boundary of acceptable continuation of not
7 giving people this treatment.

8 DR. LIPICKY: How many of those did you see?

9 DR. CALIFF: You remember I specifically said
10 in a worst case analysis, better than .001 for death or
11 death and all-cause hospitalization would do it for me
12 regardless.

13 DR. LIPICKY: Well, but your comment was that
14 -- and we accept your recommendation. I'm just trying to
15 understand the basis of it. Okay?

16 Your statement was that it was always there,
17 and what I see are p values that go from .002 looking
18 across the sponsor's thing -- so for one study .026, .035,
19 and .378. This is for mortality and all-cause
20 hospitalization. That's your big-deal endpoint. That's
21 the nominal p values, uncorrected for anything including
22 multiplicity and having been retrospective.

23 DR. CALIFF: Those were for individual studies.

24 DR. LIPICKY: You made the statement that it's

1 really there, you really think it's there a lot, and I'm
2 wondering how you made that decision.

3 DR. KONSTAM: Just following up on what Rob
4 said, I guess the single thing in the data set that makes
5 me feel most comfortable that 240 is correct is the overall
6 survival data.

7 Now, then you ask the question, what kind of
8 statistical correction would you do to that survival data
9 given the fact that it's not a specified endpoint? I have
10 no idea how to answer that from a mathematical viewpoint.

11 DR. LIPICKY: So, you are saying you're
12 comfortable with 240 for different reasons than Rob said he
13 was comfortable with 240.

14 DR. KONSTAM: I thought he said the same thing.

15 DR. LIPICKY: No. He said it was mortality and
16 all-cause hospitalization. You're saying mortality.

17 DR. CALIFF: No. I said either one, but
18 mortality being the strongest.

19 DR. LIPICKY: The mortality being the
20 strongest?

21 DR. CALIFF: Sure. How can you ignore it?

22 DR. LIPICKY: We really are back to square one.

23 DR. KONSTAM: Both.

24 DR. MOYE: This is the trap that we fall into.

1 With no guidance from the investigators on how to interpret
2 secondary endpoints, we're left with trying to root through
3 this maze and it's very tough. With eight or nine of us,
4 there will be eight or nine different paths that we're
5 going to take, and it's going to be almost impossible to
6 build a consensus about this.

7 DR. KONSTAM: But, Lem, just the way I look at
8 it, I think mortality to me is such a big deal, and that's
9 what Rob is saying. We have this big magnitude effect with
10 a very, very small p value, and I guess normally what I
11 would do under that situation is turn to the statistician
12 and say, what is the likelihood that that's a chance
13 finding?

14 DR. MOYE: Right, so you should.

15 DR. KONSTAM: And I haven't gotten any guidance
16 from that mathematically. So, now I'm going back to
17 saying, you know what? It looks pretty big and it looks
18 like a pretty small number. It trends in the same
19 direction in every single trial, and it's not a surprise
20 from a pathophysiologic viewpoint. To me that adds up to
21 enough to be something of corroboration that the endpoint
22 in 240, of which survival was an element, is real.

23 DR. DiMARCO: Dan?

24 DR. RODEN: I wasn't going to say anything

1 more, but I feel compelled.

2 I really feel that there is no basis for making
3 a claim or including in the label the idea that this drug
4 does anything to mortality. We have criteria for
5 establishing drug effects on mortality. Those involve
6 large trials. The designs are not a secret from anybody,
7 certainly not a secret from Milton.

8 (Laughter.)

9 DR. RODEN: The notion that based on one trial
10 that includes mortality as one of its many, many composite
11 endpoints and then a bunch of other touchy-feely data,
12 which I must say makes me feel good too, we'll approve a
13 drug or we'll give it a labeling for mortality I think is
14 completely inappropriate.

15 My notion was that we feel good enough about
16 this database that the drug ought to probably be approved
17 for the management of symptomatic heart failure with the
18 idea of reducing symptoms. If you want a mortality claim,
19 there are ways to get a mortality claim, but I really feel
20 very strongly that we shouldn't entertain a mortality claim
21 at all.

22 DR. WEBER: Even, Dan, if mortality was a
23 pivotal part of the data that led us to our decision and
24 conclusion?

1 DR. RODEN: It's a very small part. Boy, it's
2 a tiny part, though.

3 DR. WEBER: Tiny but important.

4 DR. RODEN: There are hundreds of endpoints,
5 and of those hundreds of endpoints, there are tens of
6 deaths. So, the endpoint you're talking about is
7 hospitalization. You're not talking about mortality as the
8 endpoint.

9 DR. DiMARCO: Jeff?

10 DR. BORER: I want to make several points.

11 First of all, I think Marvin is right in his
12 statement of the indication for the use of the drug, that
13 it's a reduction in morbidity, the incidence of morbidity,
14 whatever, because I agree that death is the worst morbid
15 event you can have. And I don't think there are data here
16 that allow us to support an independent mortality claim.
17 But I do think that morbidity defined by hospitalizations,
18 which I think is a pretty reasonable operational
19 definition, of which mortality is the worst example, has
20 been reasonably shown to be reduced by this drug.

21 Now, in terms of the supporting evidence, it's
22 true, you could look at these trials and it may be correct
23 to say -- I don't think it is -- well, you know, they
24 looked at them with no rhyme or reason, everything is

1 secondary, it's retrospective, it's this and that, and
2 therefore it doesn't work. I would suggest a slightly
3 different way of looking at what we've seen here today.

4 We have a large set of data from several
5 different centers, many sites, and in addition to whatever
6 analyses the sponsor decided to do or the investigators
7 decided to do, which maybe they did -- I don't think they
8 did -- to make themselves look better, the FDA came in and
9 said, well, here's this database. We want these analyses
10 done. So, go do these. Maybe they're different.

11 In fact, they are different than the analyses
12 that the sponsor chose to do. They may be analyses which
13 are more difficult to get a positive answer with, perhaps a
14 little bit harder in terms of the type of endpoints, more
15 conservative. They're the kinds of endpoints Rob was
16 talking about.

17 When those analyses were done, coming down as a
18 deus ex machina out of the sky, the results are positive,
19 as were the results when the sponsor did whatever analyses
20 the sponsor wanted to do.

21 I look at, for example, study 220, which I
22 don't suggest by itself should stand alone as the study,
23 but if we correct for 10 other endpoints that were looked
24 for here, we still have a p value of p less than .02 or

1 something like that. I think that's pretty good.

2 I think that one has to look at the consistency
3 of the data across the entire package we've seen. I don't
4 like the methods that we used for some of the studies. I
5 don't like some of the analyses that were done. I share
6 some of Lem's concerns about the way things were done and
7 the way they shouldn't have been done. I think all that's
8 true.

9 But in the face of that, we're looking at an
10 extraordinarily consistent database. I find that
11 compelling and I find it extraordinarily consistent with
12 regard to what I think is a very important endpoint, and
13 that is major morbidity defined by hospitalization,
14 supplemented by the worst morbid event you can have which
15 is death.

16 So, for that reason, I think that the NDA
17 supports the approval of the drug for that indication.

18 With regard to symptomatic heart failure, maybe
19 yes, maybe no. The data certainly trend in favor of
20 symptom reduction, but I'm not totally convinced by that.
21 But at least they trend in the right way to help support my
22 belief that the major morbidity is reduced.

23 DR. WEBER: And how would you express that or
24 define it, Jeff?

1 DR. BORER: How would I define what?

2 DR. WEBER: The indication.

3 DR. BORER: For the reduction in major
4 morbidity as measured by hospitalizations and death.

5 DR. DiMARCO: Cindy?

6 DR. GRINES: I'd like, I guess, to say that in
7 my opinion we approve this based on study 240, and I think
8 that the indication for the drug should be based on the
9 primary endpoint of 240 which is a combination of death and
10 progression of heart failure. As we've all been talking,
11 we're really swayed a lot by the mortality, and in 240
12 mortality alone was significant. The combined mortality
13 from all these trials is highly significant.

14 I think that it's not consistent with previous
15 recommendations of this panel to just kick mortality out,
16 even though that was the primary endpoint. There are drugs
17 that have been approved with combined endpoints, including
18 mortality, in which there is absolutely zero difference in
19 mortality, but since it was a part of the primary endpoint,
20 it was included in labeling. So, I don't know why we would
21 change that in this particular study, particularly since
22 most of the people on the panel are very impressed with the
23 mortality differences.

24 DR. KONSTAM: The problem with that, Cindy, is

1 if you're approving it on the basis of 240 and using the
2 words "morbidity" and "mortality," then it sounds like that
3 it's clear to us that the drug reduces mortality. That's
4 what it sounds like. I can't get the wording. That's the
5 problem that I have.

6 DR. GRINES: All I know is that there are drugs
7 that have been approved in just the past couple years in
8 which mortality and other endpoints are in the label and
9 there was zero difference in mortality, no significance
10 difference whatsoever if you look at mortality
11 individually. So, why is this drug being treated
12 differently?

13 DR. DiMARCO: Dr. Temple?

14 DR. TEMPLE: Those drugs don't have a mortality
15 claim. They have a mortality mention. You could say that
16 about aspirin, for example, which in secondary prevention
17 decreases the sum of hospitalization plus death, mostly
18 hospitalization, and you have to struggle to find an actual
19 separate mortality claim.

20 But I guess if 240 is one of the main things
21 one is relying on and really nothing else, then I'm newly
22 disturbed because 240 alone, as a predominantly symptomatic
23 trial, doesn't seem persuasive on its own. What I heard
24 people saying is that they find some of these other

1 endpoints, whether Ray is right to say they were picked out
2 of the air or not quite right, persuasive even though they
3 weren't the primary endpoints of the trial because they're
4 so consistent and because their p values are in many cases
5 so small. So, I heard some people say it, but that's not
6 what I heard when the voting went around, that this was
7 entirely based on 240.

8 It was also based on a belief that you could
9 learn something from those other trials. I have to say, if
10 that's not really not true, I'm distressed by what we've
11 been told because we're going to have difficulty acting on
12 it I think.

13 DR. BORER: It's true for me.

14 DR. TEMPLE: For us to approve a claim solely
15 on the basis of 240, one study in a symptomatic
16 circumstance with a sort of marginal value, depending on
17 how you do it, would be an unpleasant precedent for me
18 personally. But that isn't what I heard people saying. I
19 heard them saying they saw things in those other studies
20 that should be considered persuasive, not perfect. We all
21 know the flaws, but that there was information from those
22 studies, which were all well-controlled studies by the way,
23 that meant something.

24 How to exactly write the claims I don't think

1 is going to as all that actually.

2 DR. DiMARCO: Ray?

3 DR. LIPICKY: Well, I just want to defend
4 myself for a moment. The all-cause hospitalizations and
5 mortality appeared for the first time in November of 1996
6 in a letter that you wrote to them. It never appeared
7 anywhere in any protocol, any analytical plan, or any
8 correspondence prior to that time. So, if that is the
9 basis of feeling comfortable, it is as retrospective as I
10 can ever dream of something being retrospective.

11 DR. TEMPLE: But, Ray, wasn't there a secondary
12 endpoint in many or all of the studies --

13 DR. LIPICKY: No, sir.

14 DR. TEMPLE: Hold on. I didn't finish my
15 question. I'd like to. May I? Do I have permission?

16 Wasn't there an endpoint of death plus
17 hospitalization probably cause-specific plus increased use
18 of --

19 DR. LIPICKY: No, sir.

20 DR. TEMPLE: Just in 240.

21 DR. LIPICKY: Yes.

22 DR. TEMPLE: We know that was true in 240.

23 DR. LIPICKY: Yes.

24 DR. TEMPLE: I'd like confirmation from the

1 sponsor on that.

2 DR. LIPICKY: Well, I copied the protocols.
3 They're in my review -- or not review -- my memo. The
4 protocols are copied exactly verbatim. You won't find
5 those words.

6 DR. TEMPLE: You won't find all-cause, I'm sure
7 of that.

8 DR. LIPICKY: No. You won't find a combined
9 endpoint of death plus something anywhere.

10 DR. TEMPLE: Except in 240.

11 DR. LIPICKY: Except for 240. That had a
12 combined endpoint primary. You will not find a combined
13 anything anywhere, primary or secondary, in any other
14 protocol.

15 DR. PACKER: Ray, to be precise, each one of
16 the U.S. multi-center protocols had hospitalizations for
17 cardiovascular causes as its secondary endpoint.

18 DR. LIPICKY: Death plus.

19 DR. PACKER: Death should always be combined
20 with hospitalization as a worst case.

21 DR. LIPICKY: Terrific. So, you just didn't
22 write well.

23 All I'm saying is it is not anywhere written
24 down.

1 DR. PACKER: You can't take the worst case out
2 of analysis of a non-fatal event. You can't do that.

3 DR. LIPICKY: All right.

4 DR. MOYE: You shouldn't do it. The way to
5 ensure you don't is to say it prospectively. I agree you
6 shouldn't do it, but was that said?

7 DR. PACKER: It wasn't said but the data speak
8 for themselves.

9 DR. CALIFF: I would like to just hear what Lem
10 says. How persuasive would an unexpected mortality benefit
11 need to be for you? We haven't seen what the actual
12 statistical assessment is here for all the data on this
13 drug. We really actually haven't seen that today.

14 DR. MOYE: You really missed the May meeting,
15 didn't you?

16 (Laughter.)

17 DR. CALIFF: Yes.

18 You're saying there's no circumstance.

19 DR. MOYE: I'm saying that the finding for
20 mortality was a surprise and was not a prospectively stated
21 endpoint, and that since bad surprises can occur after good
22 surprises, that we should not accept the good surprise on
23 its face value. It should be confirmed in a trial done to
24 look specifically at mortality as the primary endpoint and

1 pushed through to the end, done in a correct way.

2 We can learn a lot of things. Discovery is
3 fine, but you shouldn't label based on discovery I think.

4 DR. DiMARCO: Well, are there any other
5 comments from anyone on the panel?

6 (No response.)

7 DR. DiMARCO: I think I'll adjourn the meeting.
8 Thank you all for coming.

9 (Whereupon, at 6:20 p.m., the committee was
10 recessed, to reconvene at 8:30 a.m., Friday, February 28,
11 1997.)

12

13

14

15

16

17

18

19

20

21

22

23

24

1

2

3